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References: **1.** Rosenberg, H. N., and Michelson, A. L.: Am. J. M. Sc. *230*:254 (Sept.) 1955. **2.** Kory, R. C., *et al.:* Am. Heart J. *50*:308 (Aug.) 1955. **3.** Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1953. **4.** Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952. **5.** Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

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Clinical Studies

The Cytotoxic Action of Carcinolytic Agents in Tissue Culture
HARRY EAGLE AND GEORGE E. FOLEY 739

It would be exceedingly helpful, of course, to have a reliable *in vitro* screening method available for testing the numerous compounds being synthesized as prospective cancer chemotherapeutic agents. The present study appears to offer a means to accomplish this. It is shown that compounds known to have anti-tumor activity in experimental animals are cytotoxic when applied directly to human cells grown in special tissue culture media; oddly enough, this applies to normal as well as to malignant tissues of human origin. The method deserves more extensive trial.

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VOLUME TWENTY-ONE NUMBER FIVE

Hypercalcemia in Malignant Disease without Evidence of Bone Destruction
CALVIN H. PLIMPTON AND ALFRED GELLHORN 750

The occurrence of symptomatic hypercalcemia in patients with extensive osteolytic metastases to the skeleton is now well recognized but from time to time one encounters marked hypercalcemia in patients who have neoplastic disease without bone metastases demonstrable even at necropsy. The authors cite a number of such cases, which present a most intriguing problem. Parathyroid tumors could be excluded. At present, no satisfactory explanation is at hand, although conjectures are offered.

Seminar on Diseases of the Pancreas

Carcinoma of the Pancreas . . . . . EUGENE E. CLIFFTON 760

Dr. Cliffton has gone to original sources for his data and the result is a refreshing reappraisal of the important problem of carcinoma of the pancreas. The points made differ in some essentials from the hackneyed descriptions of many textbooks, for example in the matter of the incidence of pain and in the differential diagnosis from carcinoma arising in the ampullary region. There is a noteworthy section on surgery of the pancreas, which may go too far for many readers. A full bibliography is appended.

Review

Renal Lesions and Acute Renal Failure in Pregnancy
WILLIAM E. OBER, DUNCAN E. REID, SEYMOUR L. ROMNEY AND JOHN P. MERRILL 781

There is much controversy and confusion concerning the significance of the renal lesions of pregnancy, and this careful study and interpretation is a welcome addition to the literature on this subject. The authors emphasize the importance, in diagnosis and prognosis, of the circumstances prior to the development of anuria in pregnancy. Acute renal failure in the course of pregnancy is usually due to tubular necrosis secondary to shock or hemolysis and is usually preventable and manageable without any sequel of progressive renal damage. Renal cortical necrosis is a less common event, an occasional complication of abruptio placentae, and is related to the presence of underlying significant nephrosclerosis which increases the tendency to infarctive coagulation necrosis. The renal lesion of toxemia of pregnancy is inconstant and inconspicuous and the oliguria is probably of extrarenal origin. Whether or not toxemia leaves any permanent impairment of the kidneys appears to depend largely upon the presence or absence of antecedent hypertensive disease and on the development of such untoward events during delivery as excessive hemorrhage or hypotension. Pyelonephritis, hyperemesis gravidarum and other renal aspects of the complications of pregnancy are also considered.

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VOLUME TWENTY-ONE NUMBER FIVE

Case Reports

Extreme Obesity Associated with Alveolar Hypoventilation—A Pickwickian Syndrome
C. Sidney Burwell, Eugene D. Robin, Robert D. Whaley and Albert G. Bickelmann 811

Wit and erudition are happily combined in this description of the syndrome of obesity, somnolence, excessive appetite, twitching, cyanosis, periodic respiration, secondary polycythemia and cor pulmonale, which has as its prototype Mr. Wardle's boy, Joe. In a well studied case the characteristic physiological derangements are described: decreased vital capacity, decreased maximum breathing capacity, alveolar hypoventilation, hypoxemia, hypercapnea and increased respiratory dead space. The essential disability is alveolar hypoventilation due to the mechanical liabilities of extreme obesity. It is demonstrated that the pulmonary and cardiac abnormalities can be relieved by weight reduction.

A Peculiar Type of Cardiopulmonary Failure Associated with Obesity
Douglas Carroll 819

Extreme obesity occasionally is accompanied by right-sided heart failure, hypercapnia and secondary polycythemia without significant structural abnormality of the heart and lungs. Two such cases are described in this report and a functional explanation, based on the mechanical handicap of extreme obesity in respiration, is offered.

Advertising Index on 3rd Cover

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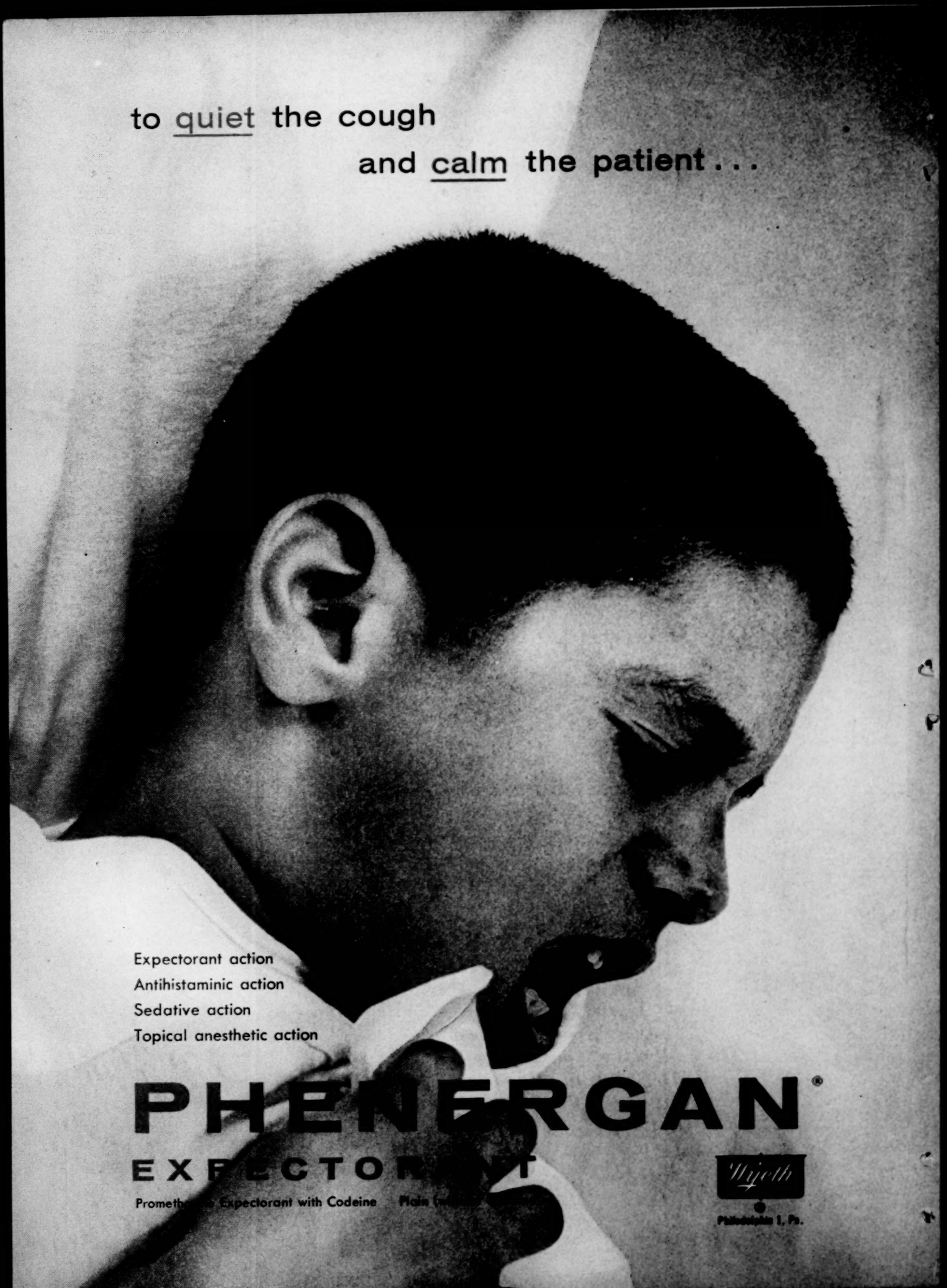
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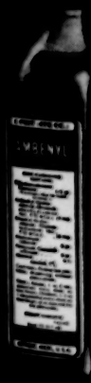
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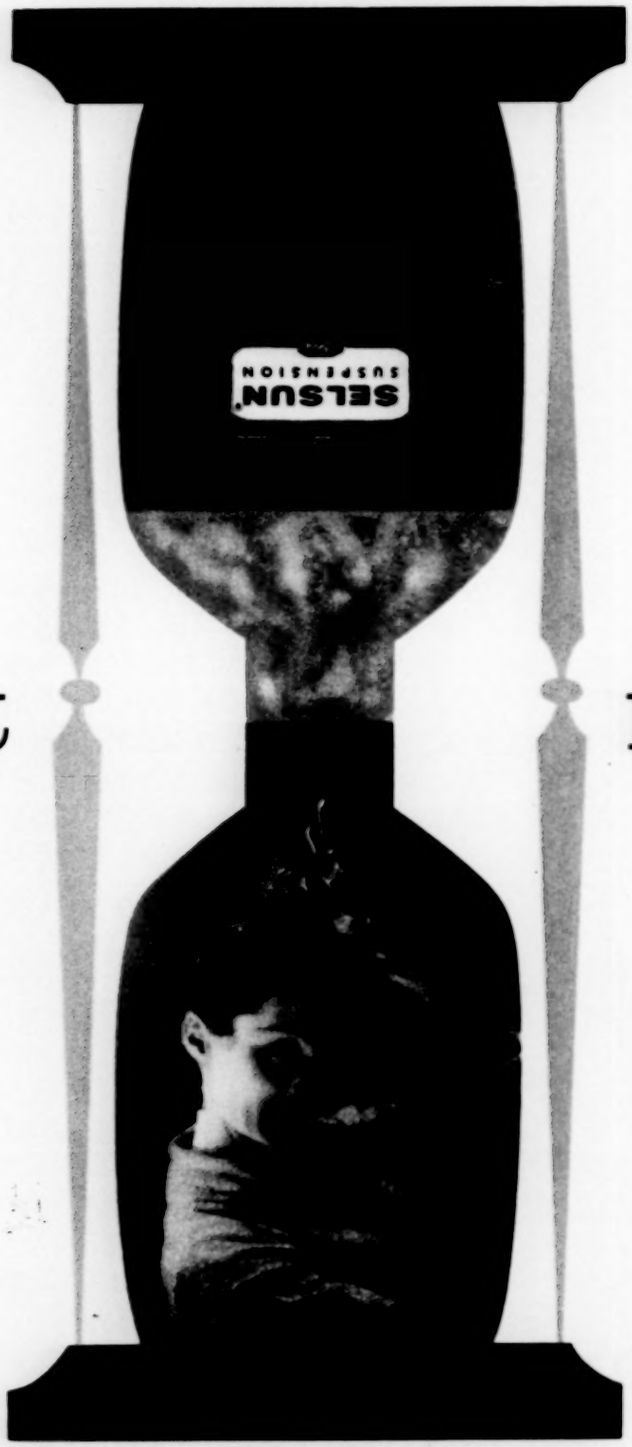
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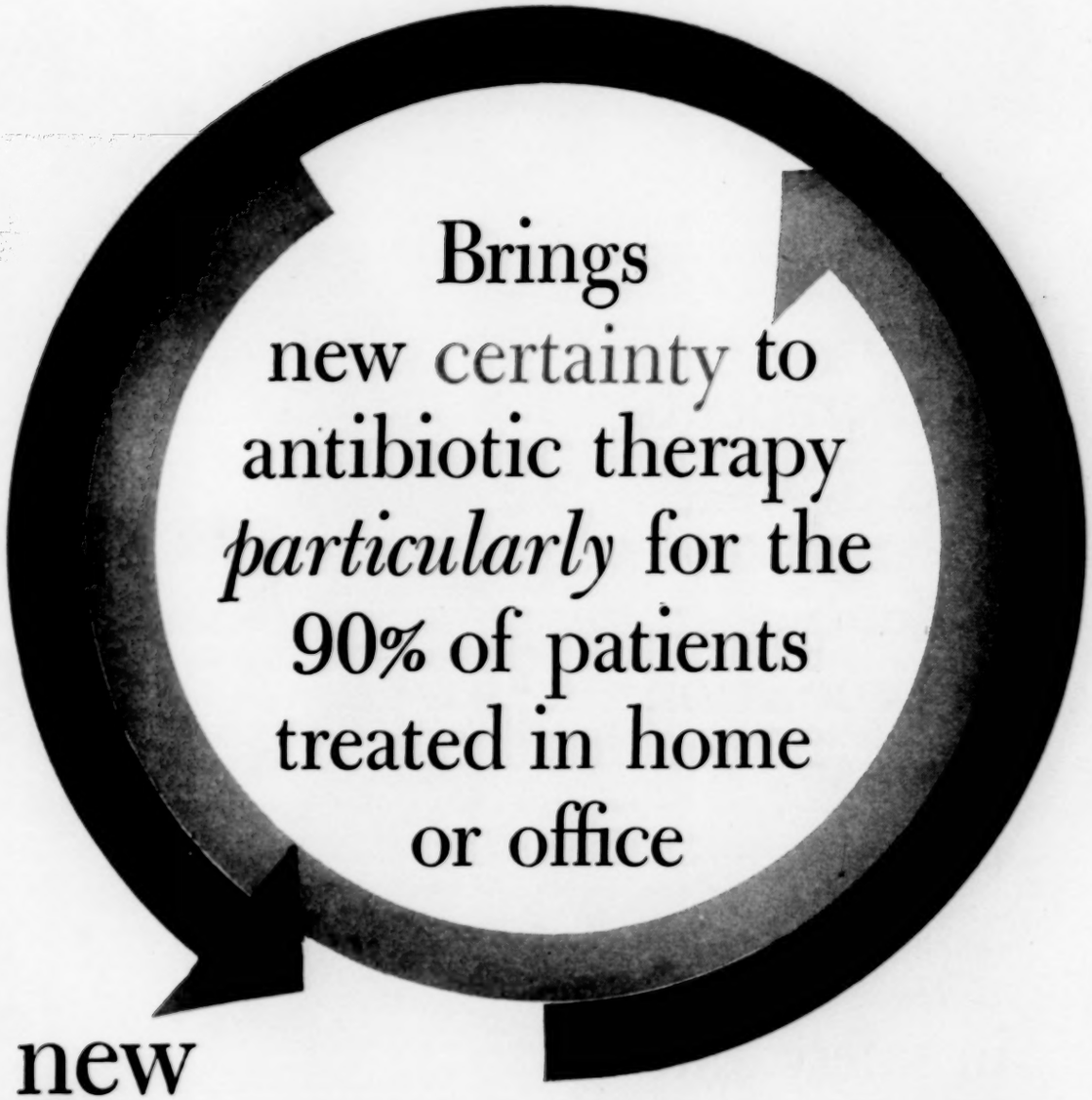
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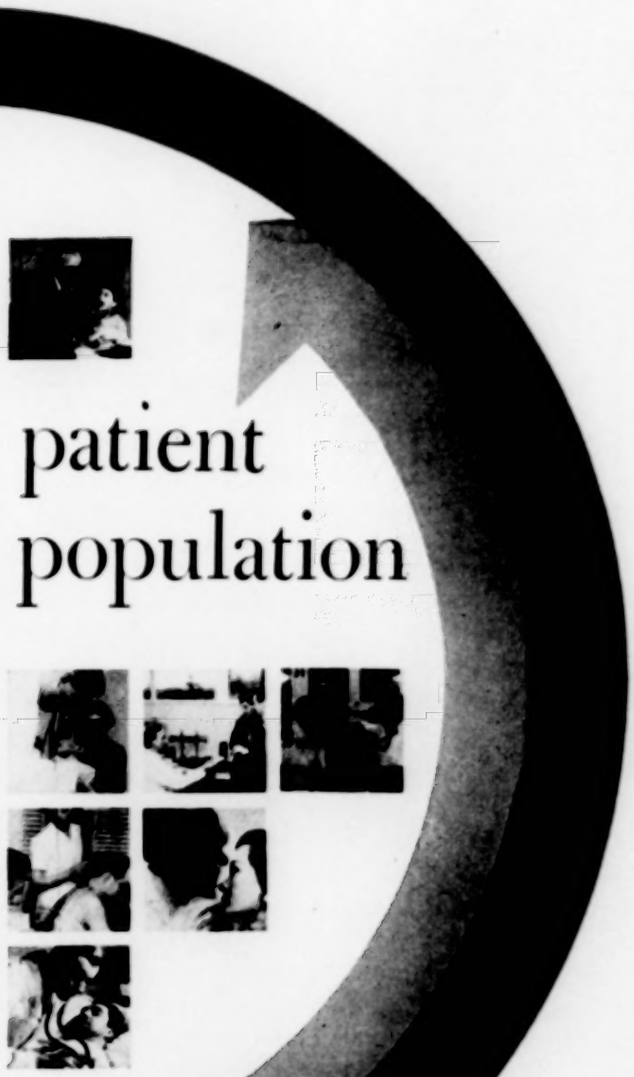
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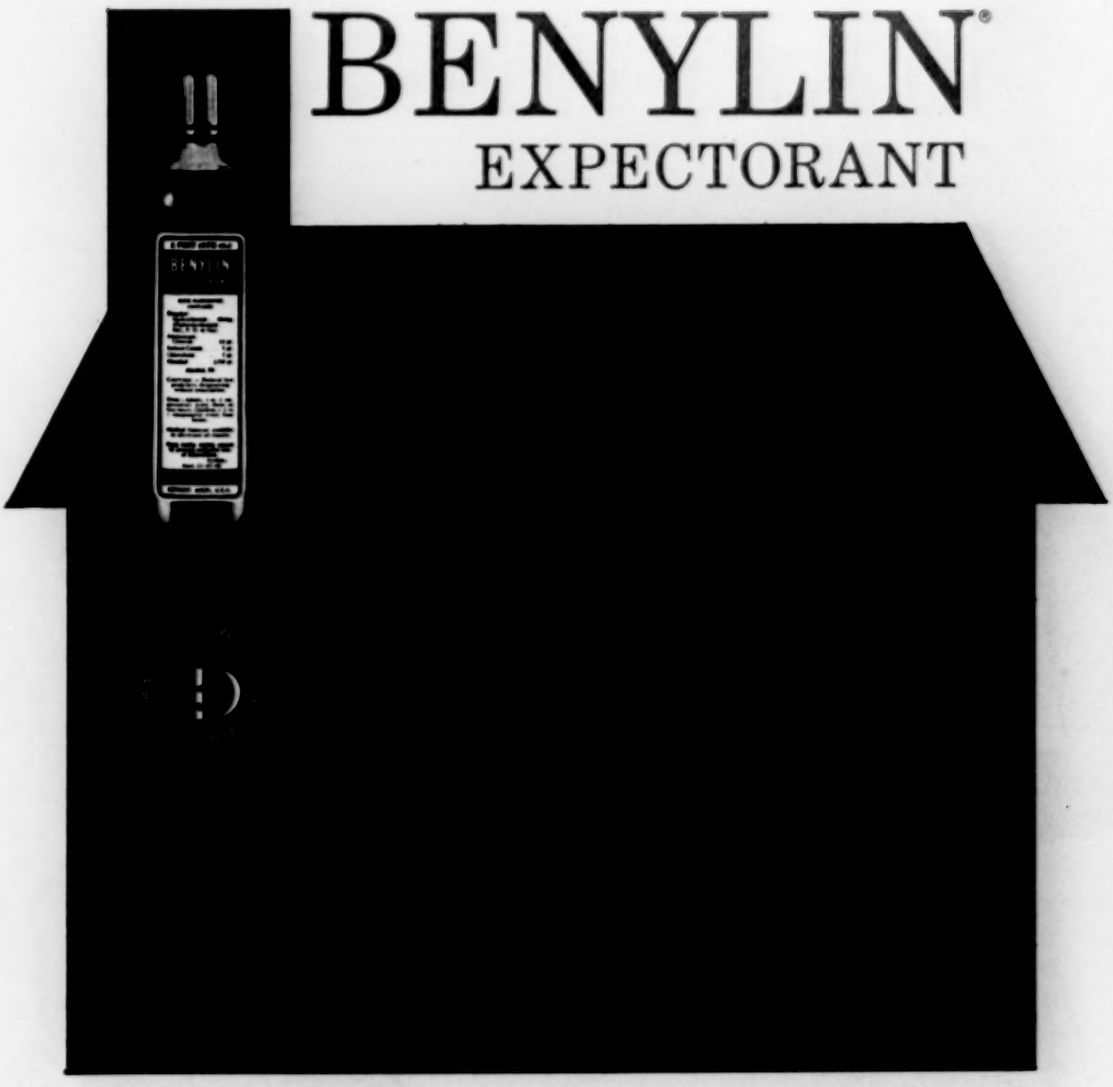
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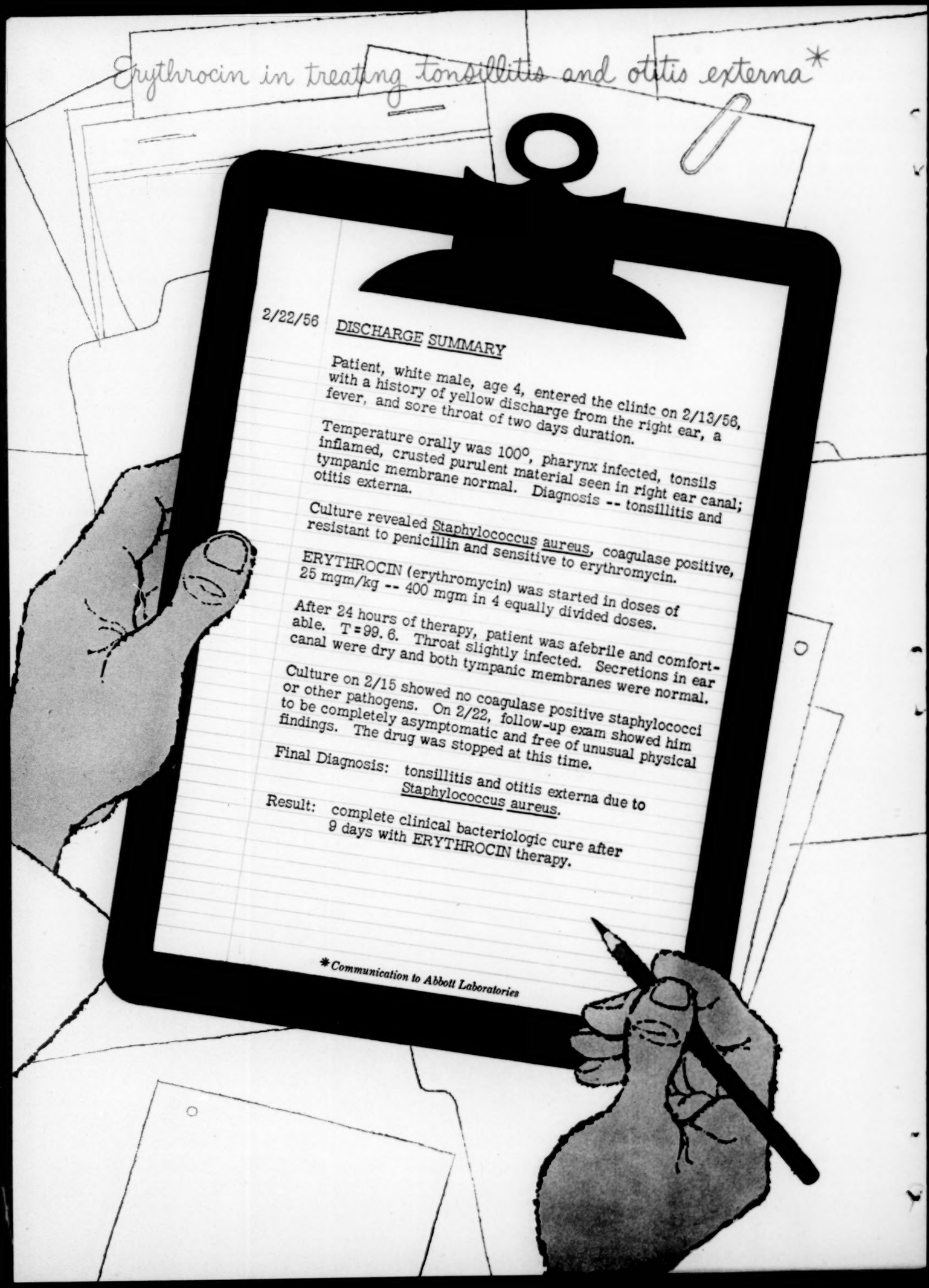
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1. Herrell, W. E., Erythromycin, Antibiotics Monographs, No. 1, p. 29, New York, Medical Encyclopedia, Inc., 1955.
Idem p. 30.

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In the development of good eating habits, medication is important, not only in initiating control, but also in maintaining normal weight.[1,2,3]

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- Methamphetamine for its anorexigenic and mood-lifting effects.
- Pentobarbital as a balancing agent, to guard against excitation.
- Vitamins B_1 and B_2 plus niacin to supplement the diet.
- Ascorbic acid to aid in the mobilization of tissue fluids.

Since Obedrin contains no artificial bulk, the hazards of impaction are avoided. The 60-10-70 Basic Plan provides for a balanced food intake, with sufficient protein and roughage.

Formula

Semoxydrine HCl (Methamphetamine HCl) 5 mg.; Pentobarbital 20 mg.; Ascorbic acid 100 mg.; Thiamine HCl 0.5 mg.; Riboflavin 1 mg.; Niacin 5 mg.

1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954).

2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).

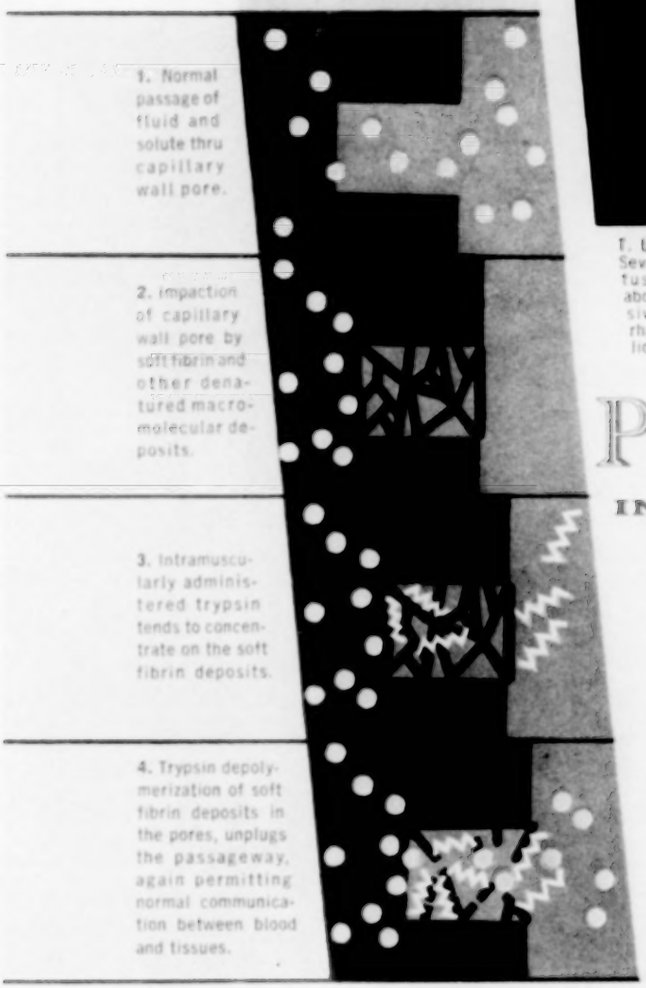
3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

Write for 60-10-70 Menu pads, weight charts, and samples of Obedrin.

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the "MECHANICAL" BARRIER
in TRAUMA *with inflammation and edema*





T. L., 26 year old white male. Severely beaten. Multiple contusions and marked edema about the face and head. Massive subconjunctival hemorrhages in both eyes. Both eyelids markedly edematous. injections of PARENZYME, every 12 hours. Some decrease of edema after 18 hours. After 36 hours, both eyes were open. After 96 hours, edema fluid and hemorrhage resorbed, contusions healed, treatment completed.

PARENZYME®

INTRAMUSCULAR TRYPSIN

alters the chemical and enzymatic phase of circulatory stasis in acute edematous and inflammatory conditions. Local circulation is re-established permitting all physiologic processes of repair to proceed unimpeded.[1] Edema fluid and necrotized tissue are resorbed, pain is quickly reduced, the inflammatory process is controlled and reversed with speeding of the healing process.[2,3,4]

Menkin's concept[5] is that the local circulation is cut off in these conditions by soft fibrin and other denatured macromolecular deposits clogging the capillaries, lymphatics and intercellular tissue spaces.[6,7] The degree of the fibrinogen to fibrin polymerization is not such as to make it comparable with the fibrin of a fixed, formed clot.

PARENZYME, the first parenteral proteolytic enzyme, has a direct depolymerizing effect on the soft fibrin and other macromolecules which form a mechanical barrier around the injured area.[8]

INDICATIONS: The cardinal indication for PARENZYME is acute inflammation; traumatic wounds, skin ulcers, vascular disorders, ophthalmic inflammations.

DOSAGE: 2.5 mg. (0.5 ml.) intragluteally q. 6 h. until improvement results; q. 12 h. thereafter. RECOMMENDED METHOD OF INJECTION: Very slowly intragluteally. SUPPLIED: 5 ml. multiple-dose vials (5 mg. trypsin/ml.).

The film, CLINICAL ENZYMOLOGY, is available for showing at all medical meetings upon request. And be sure to watch for the Med-Audiographs, a series of recorded clinical discussions.

REFERENCES:
1. Wildman, C. J., Angiology, 6:473, 1955. 2. Seligman, B., Ohio State Med. J. 51:442, 1955. 3. Golden, H. T., Clinical Med. 2:583, 1955. 4. Golden, H. T., Delaware State Med. J. 26:267, 1954. 5. Menkin, V., Dynamics of Inflammation, New York, MacMillan Company, 1950. 6. Innerfield, I., Surgery 36:1090, 1954. 7. Campagna, F. N. and Hopen, J. M., Delaware State Med. J. 27:50, 1955. 8. Martin, G. J., Exper. Med. & Surg. 13:156, 1955.



PRODUCTS OF ORIGINAL RESEARCH

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toss father time into a tailspin

with HESPER-C

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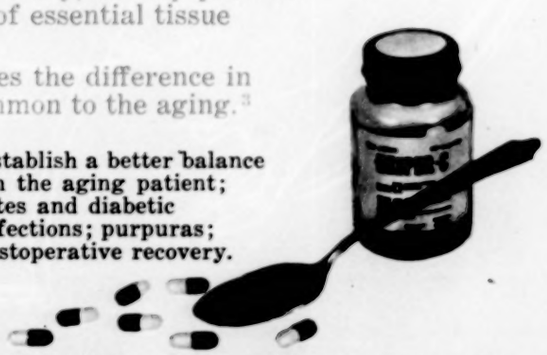
Evidence of poor tissue nutrition is often already present in the aging patient, and poor capillary status further aggravates tissue starvation.

Some common symptoms of the geriatric patient, indicative of capillary fault:[1]

- easy bruising
- difficult healing
- muscle and joint pains
- gingival and dental complaints
- tendency to bleed from skin and mucous membranes
- susceptibility to infection
- hematuria
- epistaxis

HESPER-C provides essential support for the nutrient supplying vascular termini, restoring and maintaining normal capillary permeability, to help prevent hemorrhage and enhance utilization of essential tissue nutrients and metabolites.[2]

Adequate intake of HESPER-C makes the difference in mitigating the effects of ailments common to the aging.[3]



Indications: Routine preventive geriatrics – to establish a better balance of tissue repair versus tissue destruction in the aging patient; cardio- and cerebrovascular diseases; diabetes and diabetic retinopathy; epistaxis; upper respiratory infections; purpuras; arthritis; fractures. HESPER-C hastens postoperative recovery.

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HESPER-C provides 100 mg. of fully active hesperidin concentrate plus 100 mg. ascorbic acid per capsule or per teaspoonful (5 ml.). DOSAGE: No less than 6 capsules or teaspoonfuls daily. Maintenance dose 4 capsules or teaspoonfuls daily. SUPPLIED: Liquid in bottles of 4 oz. and 12 oz. Capsules in bottles of 100 and 1000.

REFERENCES: 1. Gale, E. T. and Thewlis, M. W.: Geriatrics 8:80, 1953. 2. Martin, G. J. (Editor): Hesperidin and Ascorbic Acid. Naturally Occurring Synergists. Basel, Switzerland. Messrs. S. Karger, 1954. 3. Drezner, H. L., et al.: Amer. Pract. & Dig. of Treatment 6:912, 1955.

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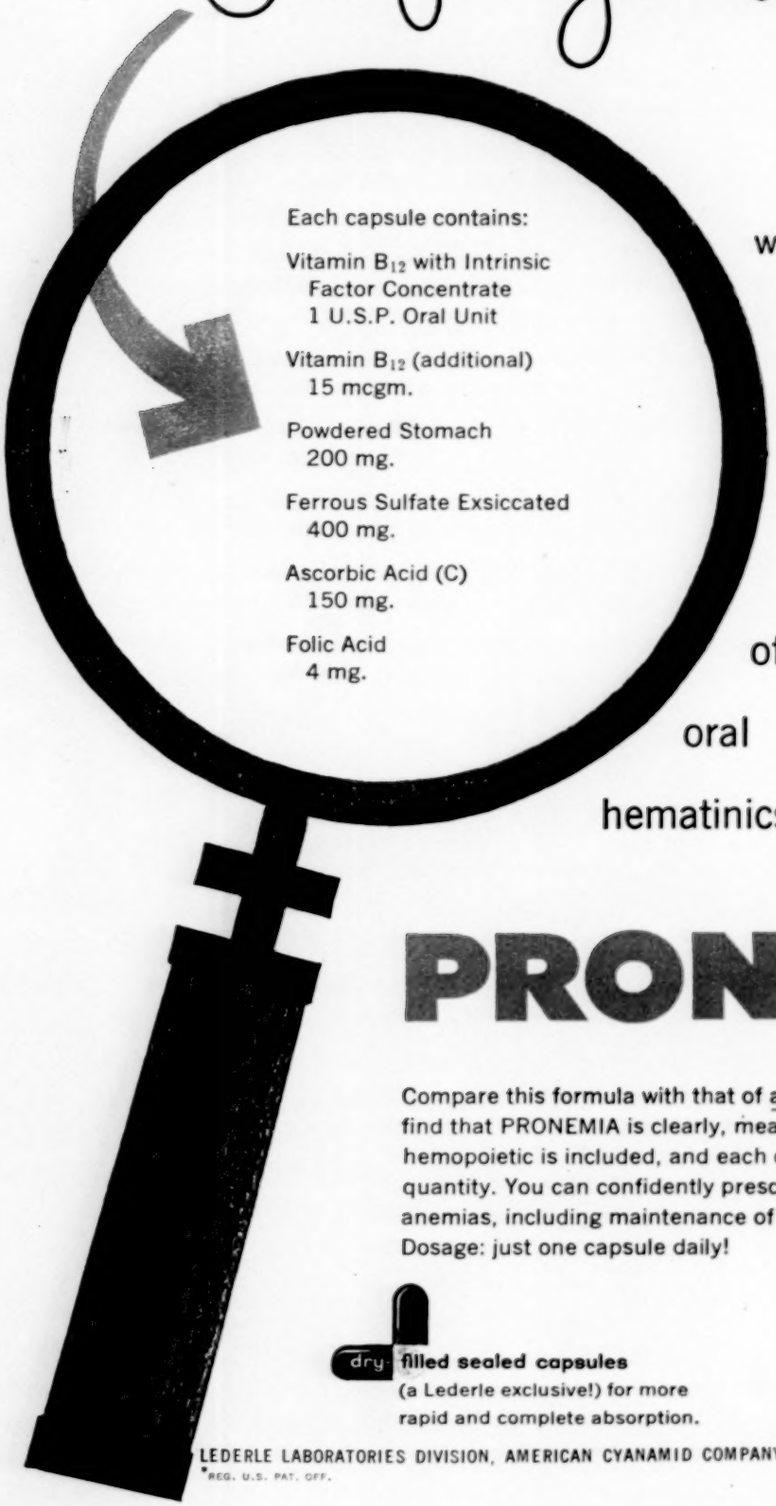
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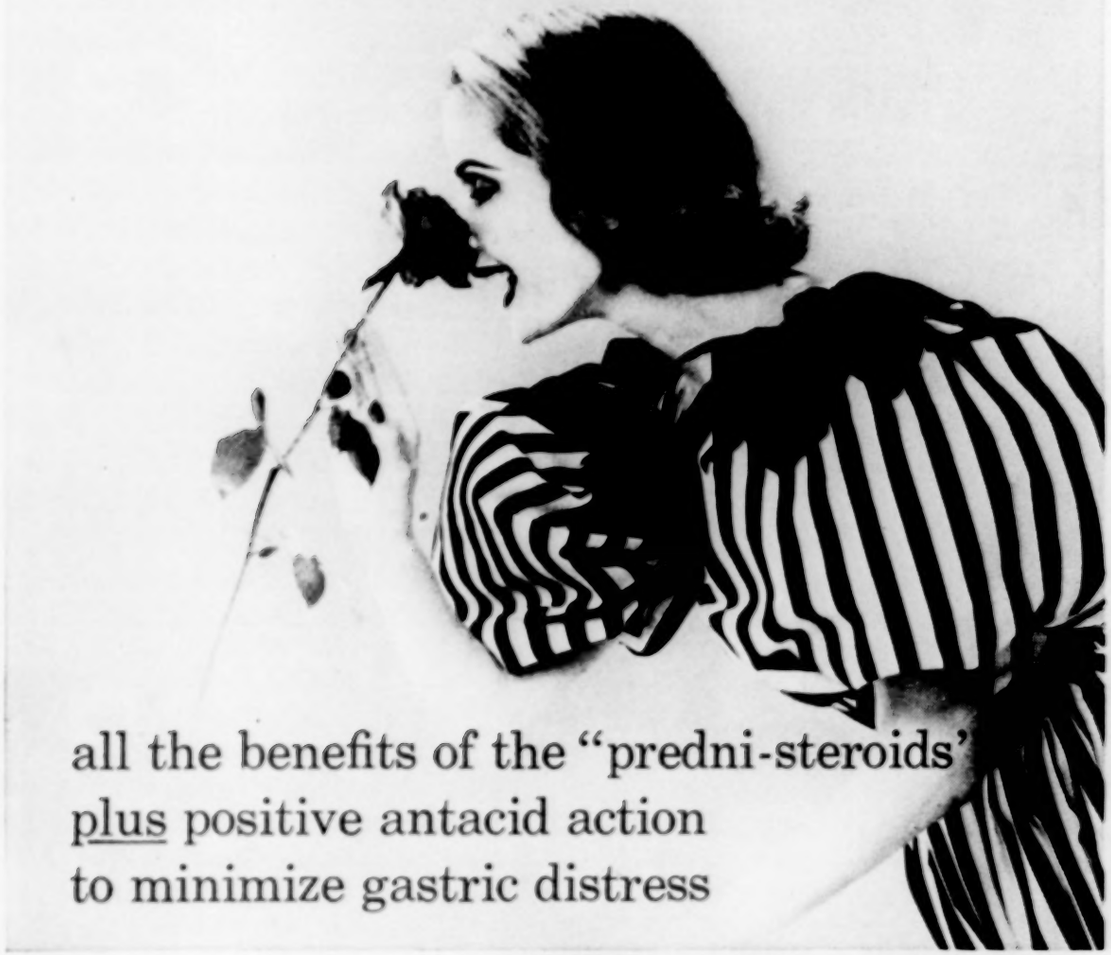
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References: 1. Boland, E. W., *J.A.M.A.* **160**:613 (February 25) 1956. 2. Margolis, H. M. *et al.*, *J.A.M.A.* **158**:454 (June 11) 1955. 3. Bollet, A. J. *et al.*, *J.A.M.A.* **158**:459 (June 11) 1955.

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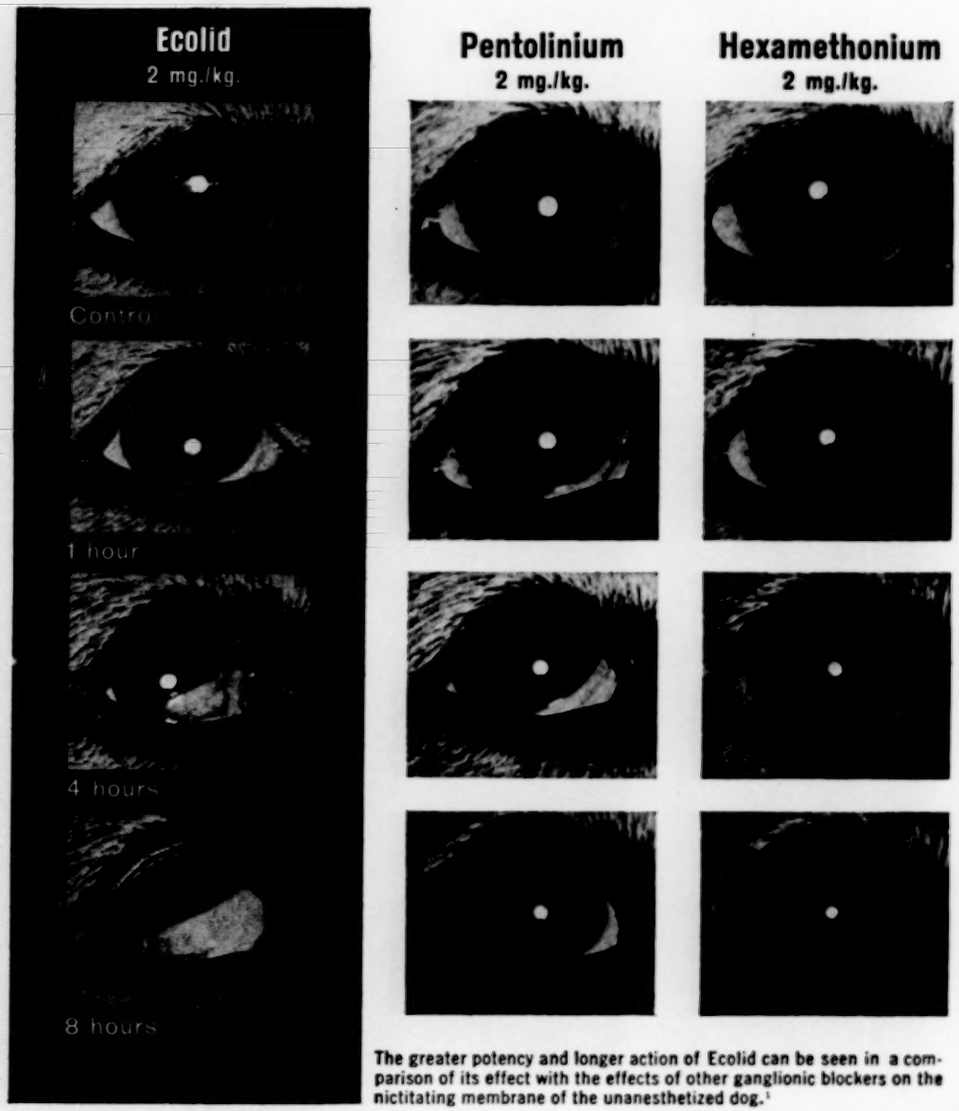
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1. Plummer, A. J., Trapold, J. H., Schneider, J. A., Maxwell, R. A., and Earl, A. E.: J. Pharmacol. & Exper. Therap. *115*:172 (Oct.) 1955. 2. Grimson, K. S.: J.A.M.A. *158*:359 (June 4) 1955. 3. Smith, J. R., and Hoobler, S. W.: Univ. Michigan M. Bull. *22*:51 (Feb.) 1956. 4. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Circulation *11*:733 (May) 1955.

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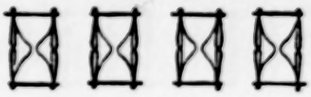
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1. Groskloss, H. H. et al: Bonadoxin®: a unique control for nausea and vomiting of pregnancy. Clin. Med. 2:885 (Sept.) 1955. 2. Tartikoff, G.: The antiemetic function of Bonadoxin in the nausea and vomiting of pregnancy. Clin. Med. 3:223 (Mar.) 1956.

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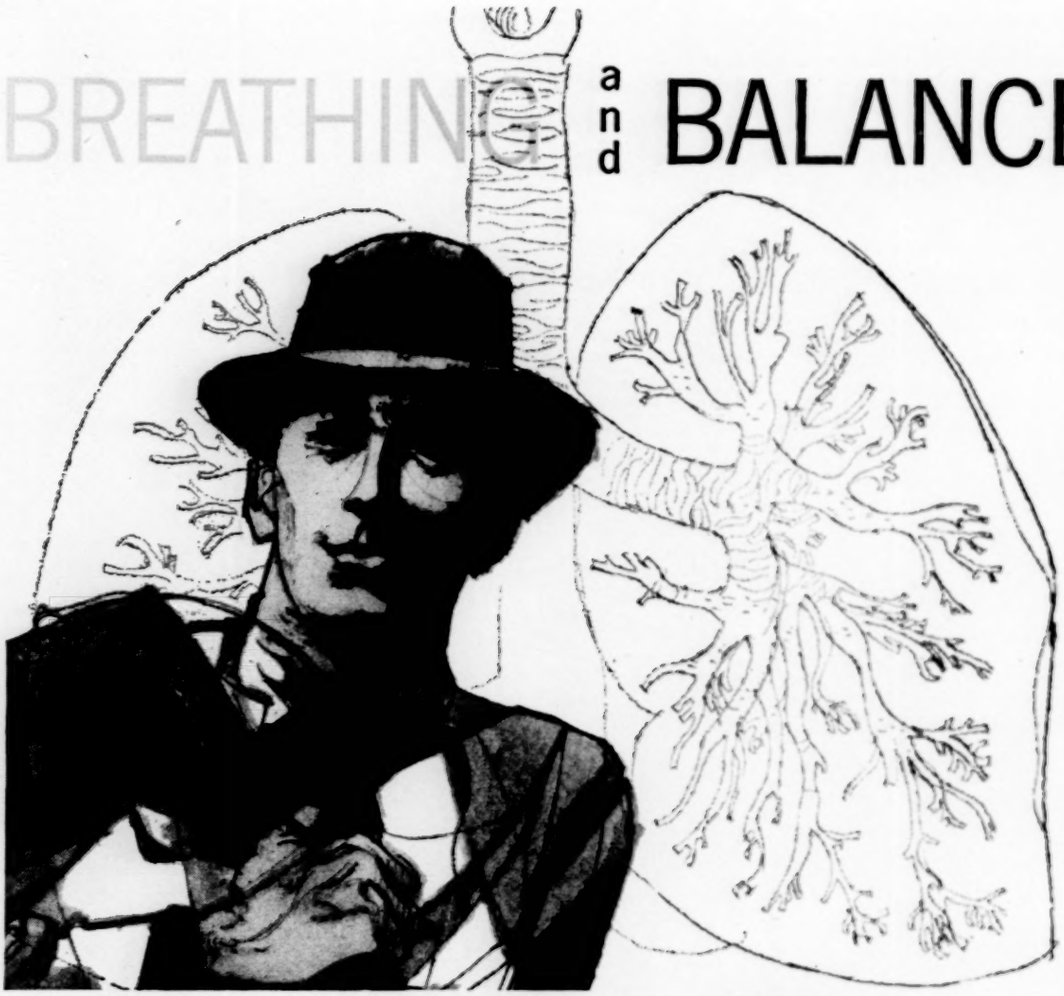
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*Schwartz, E.: New York J. Med. 56:570, 1956.

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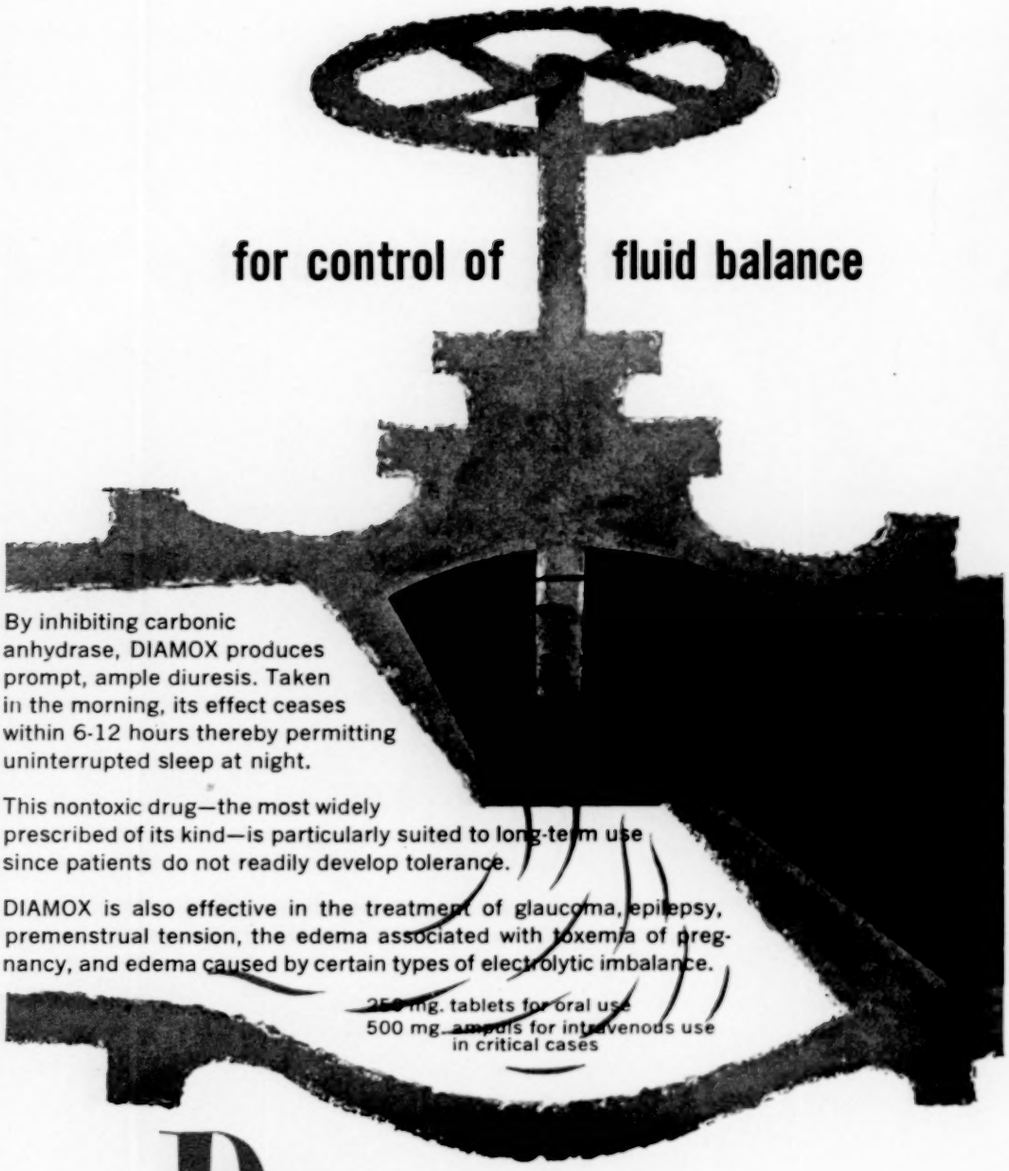
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*Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Washington, D. C., National Academy of Sciences—National Research Council, 1952, p. 21.

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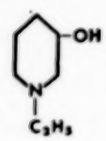
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(1) Zimmerman, F. T.: *New York J. Med.* 55:2338, 1955. (2) Drake, F. R.: *Am. J. M. Sc.* 230:98, 1955. (3) Levy, L., & Shanbrom, E.: *Arch. Int. Med.* 97:599, 1956.

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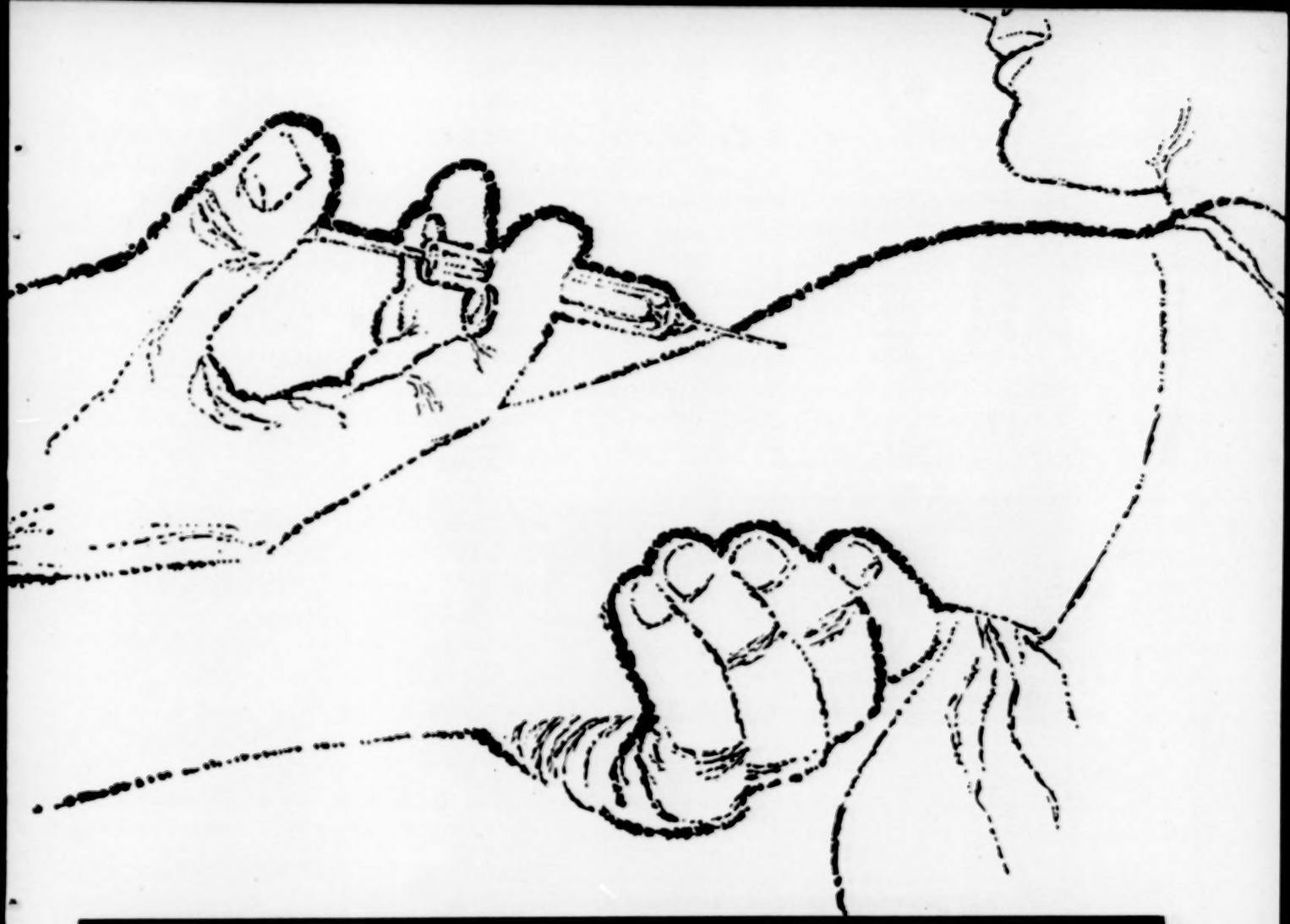
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1. New and Nonofficial Remedies. J.B. Lippincott Co., Philadelphia, 1956, p. 328. 2. Osol, A., and Farrar, G.E., Jr.: The Dispensatory of the United States of America. J.B. Lippincott Co., Philadelphia, 1956, pp. 808-809.

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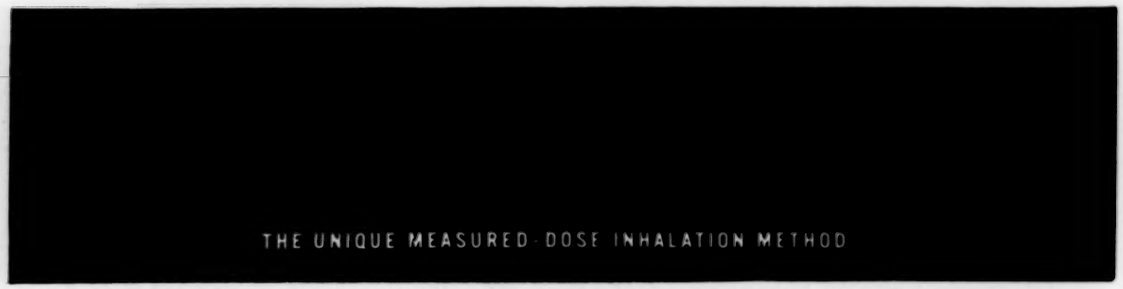
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References: 1. Boland, E. W., *J.A.M.A.* **160**:613 (February 25) 1956. 2. Margolis, H. M. *et al.*, *J.A.M.A.* **158**:454 (June 11) 1955. 3. Bollet, A. J. *et al.*, *J.A.M.A.* **158**:459 (June 11) 1955.

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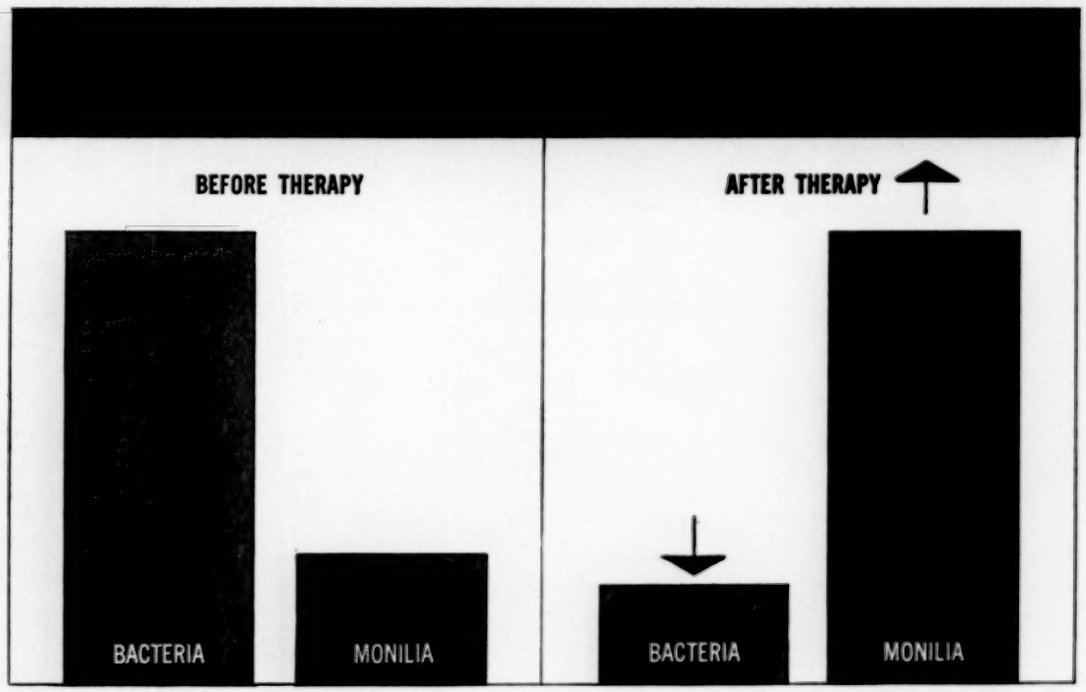
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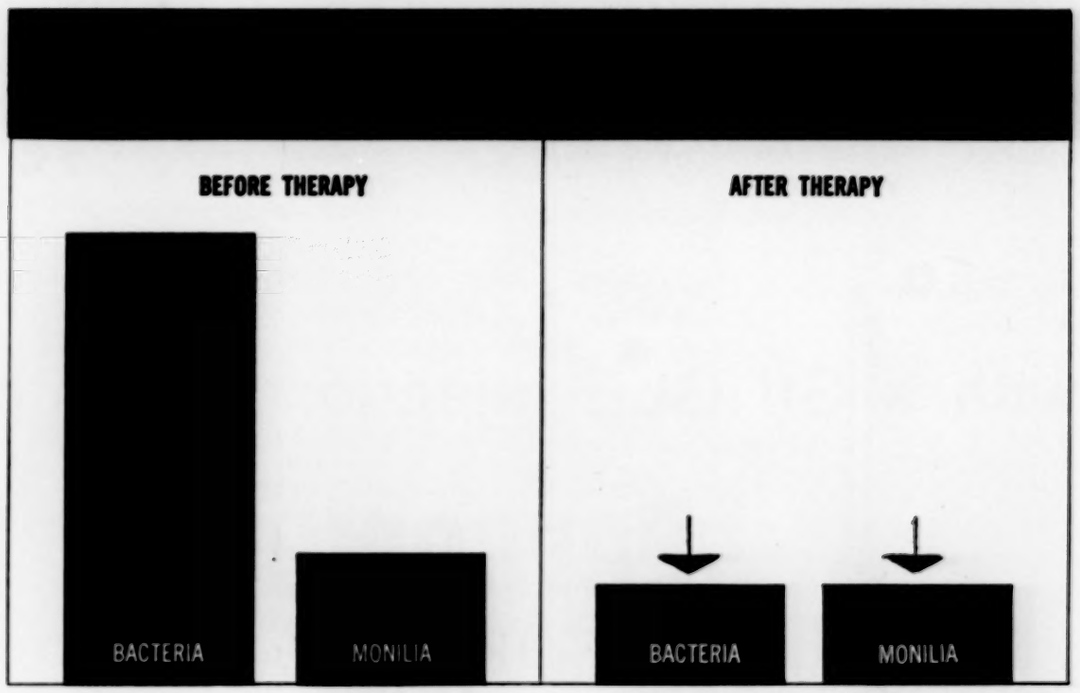
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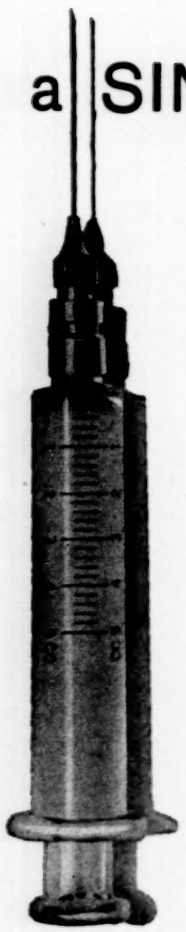
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1. Frawley, T. F., and Forsham, P. H.: J. Clin. Endocrinol. *11*:772 (July) 1951.

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**Menger, H. C.: New York J. Med. 56:1279, 1956*

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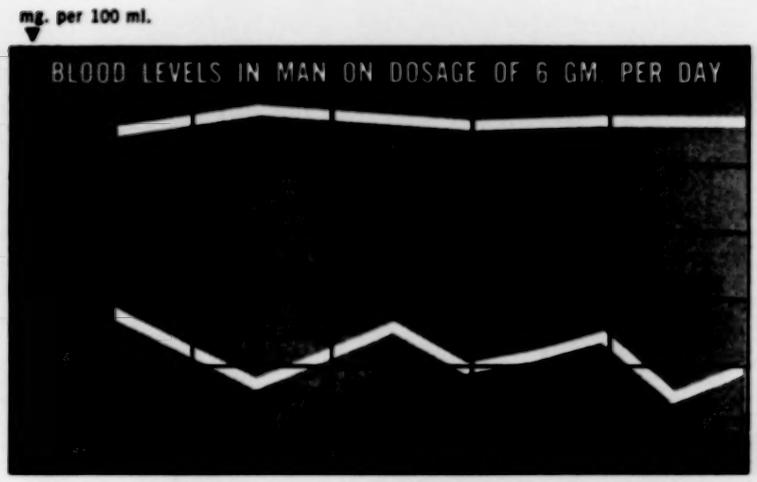
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The American Journal of Medicine

VOL. XXI NOVEMBER, 1956 No. 5

Foreword

GREATER diagnostic acumen, extension of the life span and increased exposure to environmental carcinogens are among the important factors to account for the rising frequency of cancer. Concomitantly, despite improvements in methods of early diagnosis and advances in treatment by surgery and radiation, the problem of medical management of disseminated neoplastic disease has also grown. The first therapeutic regimen which had a significant effect on the course of a generalized neoplasm was androgen deprivation in prostatic carcinoma. This important contribution made by Huggins and his associates in 1940 stimulated clinical interest in the potentialities of hormone modification for the therapy of cancer which remains fresh and strong today. The symposium which follows presents a critical appraisal of the current status of Hormones and Cancer.

This is a particularly timely subject to be considered by physicians because of their responsibility in the purely medical treatment of patients with tumors which are affected by hormone administration, as well as in the selection and postoperative care of patients in whom hormone ablative procedures are carried out. In the clinical discussions, attention will be focused on carcinoma of the prostate and of the breast. An indication of the size of the problem presented by these two tumors is given by statistics derived by the Connecticut State Department of Health[1] which show that twenty-nine new cases of prostatic cancer per one hundred thousand men are diagnosed annually and that the annual incidence for carcinoma of the breast in women is sixty per one hundred thousand. Twenty-one per cent of all patients with cancer of the prostate survive for five years after diagnosis; 46 per cent of all women with carcinoma of the breast survive for this period after diagnosis has been established.[2] It is apparent that these diseases occur frequently and that their biology is such that clinical cure is achieved in less than one-half of the patients. To what extent can the manipulation of hormones affect the course of these cancers and when should what be done?

Dr. Kirschbaum's paper introduces the discussion of hormones and cancer with particular emphasis on their importance in tumorigenesis as shown in laboratory animals. Attention should be given to the concept of tumor dependence and autonomy which has emerged from this experimental work since the success of hormone modification in the treatment of human cancers appears to rest on this issue. Dr. Kirschbaum brings out the interesting fact that endocrine ablations or the administration of sex hormones do not affect the natural history of spontaneous cancer of the breast in mice; these measures, however, if initiated early in the life of mice can prevent the development of tumors in strains which have a high spontaneous incidence of the disease.

Dr. Hertz assesses the importance of hormone stimulation in the genesis of cancers in hormone-dependent organs in man and finds that there is little evidence to indicate that this is a major factor. His lucid summary of the physiologic effects of the gonadal steroids provides a firm foundation for recognizing the "side effects" of hormone therapy in patients with cancer. Particularly valuable is the discussion of the metabolic actions of the hormones since these are of very real importance in explaining therapeutic benefits which may occur even when there is no apparent tumor inhibition.

The paper by Dr. Dorfman provides an essential background for the proposed rationale of adrenal and pituitary ablation. The metabolism of the sex hormones and adrenal cortical

[1] OSBORN, STANLEY, H. Cancer in Connecticut 1935–1951. Connecticut State Department of Health, Hartford, Connecticut, 1955.

[2] GRISWOLD, M. H., CUTLER, S. J. and EISENBERG, H. Improvements in cancer survival rates. *New England J. Med.*, 254: 1062, 1956.

steroids, the question of androgen conversion to estrogen, and the extent of androgen and estrogen secretion by the adrenal cortex are among the topics discussed by Dr. Dorfman which contribute to informed understanding of hormones and cancer.

The paper by Dr. Taylor provides a guide to the pragmatic use of androgens and estrogens in the treatment of cancer of the breast together with brief mention of his experience with adrenalectomy and hypophysectomy. The value and advantages of estrogens for the postmenopausal patient have been emphasized. The recommendations for the sequence of hormone modification in the various types of clinical problems which are seen in cancer of the breast are instructive.

Dr. Whitmore presents a comprehensive discussion of clinical aspects of prostatic cancer with emphasis on diagnosis and therapy in relationship to the natural history of the tumor. The status of androgen deprivation therapy with an evaluation of the effect of this regimen on survival time establishes its usefulness for palliation. The limited value of adrenalectomy and probably of hypophysectomy in the management of recurrent prostatic carcinoma emphasizes again the importance of tumor autonomy as the major cause of failure of hormone therapy in cancer.

The frequency of skeletal metastases from carcinomas of the prostate and breast is very high and the associated disturbances in mineral metabolism constitute one of the major complications of disseminated cancer of the breast. Dr. Baker presents the problem of hypercalcemia instructively and relates the influence of hormones to both the genesis of the metabolic disturbance and to its treatment. The discussion of the usefulness and limitations of urinary calcium excretion studies for the evaluation of therapeutic measures in cancer of the breast introduces valuable words of caution for clinical investigators.

Dr. Kennedy presents an appraisal of the contribution of castration, adrenalectomy and hypophysectomy in the treatment of disseminated cancer of the breast. Attention is drawn to the value of ovariectomy in the premenopausal patient with metastatic cancer of the breast and the necessity for adequate ovarian radiation dosage if this technic is elected for castration. The problems of long term maintenance in the adrenalectomized patient are discussed and it is suggested that the analogous situation in the hypophysectomized individual is less difficult. It is emphasized that the place of hypophysectomy in the treatment of cancer of the breast is still being defined and it is not surprising, therefore, that Dr. Kennedy and Dr. Taylor are not in agreement on the relative merits of this procedure as compared to bilateral adrenalectomy. In any event, both point out the importance of tumor dependence on hormone as a requisite for therapeutic benefit from any of the extirpative procedures and from this it follows that such information constitutes the major criterion for the selection of patients for adrenalectomy or hypophysectomy.

Drs. Luft, Olivecrona, Ikkos, Nilsson and Ljunggren who pioneered in the use of hypophysectomy for the treatment of cancer of the breast present a conservative and critical summary of their own experience. Histologic study of the sella turcica at necropsy revealed that pituitary removal was incomplete in a significant number of cases. In spite of this, objective regression of the tumor could occur. Whether or not the presence of pituitary tissue was an important factor in any of the therapeutic failures or in the duration of remissions achieved cannot be evaluated. The finding does emphasize, however, that complete hypophysectomy is technically difficult. The results in a small number of patients with prostatic cancer are provocative and even though the collected experience cited by Dr. Whitmore is not encouraging further evaluation would appear to be indicated.

At the present time there is agitation in some clinics to initiate radical endocrine ablative procedures early in the natural history of certain cancers of the breast because the prognosis is recognized to be poor. The evidence which has been summarized so ably in the present symposium would not appear to support such a program. It is, perhaps, well to reemphasize a fundamental fact regarding hormones, namely, that these agents act primarily as quantitative regulators of inherent cellular functions; they do not produce qualitative changes in the metabolism of the cell. This basic characteristic of the mechanism of action of hormones explains why the results of hormonal therapy of human cancer, irrespective of initial success, ultimately prove to be inadequate.

ALFRED GELLHORN, M.D.
Presbyterian and Francis Delafield Hospitals
New York, N. Y.

Symposium on Hormones and Cancer Therapy

Endocrine Aspects of Experimental Neoplasia*

ARTHUR KIRSCHBAUM, M.D.
Houston, Texas

HORMONES, carcinogenic chemicals, ionizing radiations and viruses have been associated with the experimental induction of neoplasms in animals. Although certain similarities in the natural history of cancers of man and animals (for example, cancer of the breast) have been demonstrated, in other instances it is difficult to reconcile the experimental with the clinical. Studies in the biology of cancer are contributing towards the management of human neoplastic disease. For example, the description of postcastrational adenomas of the adrenal cortex[1] and their relation to the development of mammary cancer of mice[2] probably contributed toward the concept of adrenalectomy as a means of withdrawal of hormone accelerating neoplastic growth.[3]

Reciprocal Relation of the Pituitary Gland and Its Target Organs in Tumorigenesis. Alteration in the balanced reciprocal relation between the pituitary gland and its target tissues may lead to the genesis of experimental neoplasms of both the anterior hypophysis and the glands whose growth is normally accelerated by its trophic hormones.[4] An excellent illustration is the induction of tumors of both the thyroid[5] and the pituitary glands[6] of mice by administration of radioiodine.

If only 50 microcuries are given to a rat and only part of the thyroid gland is destroyed, the remainder may become hyperstimulated to form adenomas. Following complete radiothyroidectomy of a mouse with 300 microcuries a pituitary tumor appears after a latent period of several months.[4,6] Such tumors can be successfully transplanted with resultant progressive growth into histocompatible, genetically related hosts if they have been thyroidectomized.[7] In spite of tissue compatibility which satisfies the usual requirements for transplantation, the pituitary tumors will not grow unless the recipients are without thyroid tissue. After several passages through such hosts the tumors attain the capacity to grow in intact mice.[7] The tumor transplants cause the intact recipient host's thyroid gland to become hyperplastic, demonstrating production of thyrotrophic hormone.[8]

Thus hypersecretion of the pituitary gland (thyroid-stimulating hormone) follows radiothyroidectomy. Adenomatous transformation then occurs in the anterior pituitary, the stimulus being hypothyroidism; cells of the adenoma secrete thyroid-stimulating hormone. The pituitary adenomas are dependent neoplasms as demonstrated by their ability to grow as transplants only if the histocompatible recipient host has been thyroidectomized. During growth as a transplanted tumor autonomy is acquired with progressive growth now appearing upon transplantation into intact hosts. The development of pituitary adenomas, which secrete thyroid-stimulating hormone, can be prevented by the administration of thyroid hormone after radiothyroidectomy.[9]

Is hormonal imbalance *per se* sufficient to induce neoplasia or are other factors required?

* From the Department of Anatomy, Baylor University College of Medicine and the University of Texas Dental Branch and the Department of Biology, University of Texas M. D. Anderson Hospital and Tumor Institute, Texas Medical Center, Houston, Texas. Investigations of the author and his collaborators providing background for writing this review were supported by grants from the National Cancer Institute, Public Health Service and the American Cancer Society.

When increased secretion of pituitary thyroid-stimulating hormone was induced by administering thiouracil, thyroid adenomas resulted but pituitary tumors were rare[4] although thiouracil blocks the formation of the thyroid hormone which suppresses thyrotrophic output of the anterior pituitary. Pituitary tumors have resulted either from the administration of thiouracil[10] or from surgical thyroidectomy[11] but radiothyroidectomy is a more efficient means of producing pituitary tumors. Most strains of mice respond to tumor induction following the administration of radioiodine. Rats have proved refractory,[12] indicating that all hosts do not respond to the same imbalance by tumor production.

Hormonal imbalance plus other factors may in some instances be required for tumor induction. Gonadectomy *per se* did not result in the development of pituitary tumors in mice of specific genetic constitution but such neoplasms developed if heavy doses of x-rays to the entire body were superimposed on the imbalance.[13] Administration of nitrogen mustard had a similar augmenting effect.

That hormonal imbalance alone can induce neoplasia is demonstrated by other experiments. Ovarian tumors can be induced by transplantation of an animal's (rat, mouse) ovary to the spleen if no functional ovary exists outside of the portal venous bed, or if adhesions do not form allowing venous drainage from the spleen into the systemic circulation.[14–16] Since the ovarian hormone produced by the ovary transplanted to the spleen is inactivated in its passage through the liver,[17,18] the host is physiologically castrate. Gonadotrophin output of the pituitary gland is increased as a result[19] and hyperstimulation of the transplanted ovary ensues. Such hyperstimulation eventuates in neoplasia. Certain of these ovarian tumors are initially hormone-dependent and can be transplanted successfully only into hosts in which the environment necessary for induction is duplicated. Thus transplantation may be successful only if grafts are made into the spleens of gonadectomized recipients.[15] On the other hand, some tumors were readily transplantable subcutaneously in intact mice.

Ovarian tumors caused by x-radiation are probably actually hormone-induced.[20] When only a single mouse ovary was radiated, the other remaining functional, no ovarian tumor appeared. If the non-radiated ovary was removed, the radiated ovary became tumorous. Radiation of both ovaries resulted in bilateral tumor development. In the absence of appreciable estrogenic secretion following ovarian radiation, the pituitary becomes hyperactive in producing gonadotrophin,[21] stimulating the remaining non-functional ovarian tissue to develop tumors which may now secrete sex steroids.

Thus in the case of both ovarian transplants to the spleen and the x-radiated ovary, high levels of gonadotrophin may be responsible for tumorigenesis. It has, however, been demonstrated that mouse ovarian tumors may develop even though the blood levels of gonadotrophin are not elevated.[21]

The administration of estrogenic hormone prevented the development of ovarian tumors by x-rays; androgens were ineffective.[22] When radiated ovaries were transplanted into intact as well as castrated male mice, ovarian tumors developed.[23] If the target tissue had been altered by x-rays, normal levels of trophic hormone were tumor-inciting. Radiated ovaries were, however, no more susceptible than normal ovaries to tumorigenesis when the gonads were transplanted into the spleen.[24]

Although functional ovarian transplants inhibit tumorigenesis postradiation,[23] this inhibiting effect wanes if grafting is postponed.[25] A force which initially inhibits tumorigenesis loses this capacity, growth then being termed autonomous. The more the neoplasm retains its relation to the forces which control its initiation, the more dependent the tumor. For example, hormonal stimulation of the breast is necessary for carcinogenesis; in at least certain instances growth as well as initiation of the neoplasm is dependent on hormonal factors.[26]

Although the age of the host did not influence ovarian tumorigenesis resulting from transplantation to the spleen,[27] older ovaries were less susceptible to tumor formation than ovaries from young mice.[28] The monkey liver was not capable of completely inactivating estrogenic hormone secreted by ovaries transplanted to the spleen[29] and tumors did not develop. Mice which became pregnant after radiation of their ovaries exhibited the same degree of ovarian tumor formation as animals which were sterile immediately postradiation, indicating that a delayed effect of radiation may be potent in tumorigenesis.[30]

Thyroid Tumors. The hyperplasia of the

mouse thyroid gland coincidental with administration of thiouracil may result in neoplasia.[31,32] After frequent transplantation of hyperplastic thyroid tissue, autonomy develops as indicated by successful transplantation into mice with intact thyroid glands.[32] The hyperplastic mouse thyroid may be transplanted but only into thyroidectomized recipients which are genetically histocompatible.[33] Since thiouracil-induced thyroid overgrowths may regress upon cessation of treatment with thiouracil, there is some question that true neoplasms are induced by administration of this chemical. The carcinogen, acetylaminofluorene, when given together with thiouracil increases the incidence of thyroid neoplasia.[34,35] However, the resulting neoplasms are dependent, growing only in hypothyroid hosts.

Whether frequent transplantation is responsible for the transformation of hyperplasia to neoplasia, or whether transplantation merely provides a longer period during which the transformation may occur, is a subject for investigation.

That thyroid-stimulating hormone is actually the tumor-inciting stimulus is suggested by the thiouracil-feeding experiments. Further evidence that this is the case has been contributed by feeding iodine-deficient diets.[36,37] With reduced production of thyroxine and consequent overproduction of pituitary thyroid-stimulating hormone, adenomas of the thyroid gland develop.

Thyroid neoplasms have been induced by the administration of radioiodine.[5] Radioiodine might create a hypothyroid state with resulting increased blood levels of thyroid-stimulating hormone inciting the residual thyroid tissue to neoplastic alteration. In instances in which the blood level might not be elevated and thyroid adenomas develop, normal levels of thyroid-stimulating hormone might be tumor-promoting as a result of alteration of the end organ. This situation would be analogous to the development of tumors in radiated ovaries although the blood level of gonadotrophin is not elevated.[21–23]

Adrenocortical Tumors. Following gonadectomy in several species (guinea pigs, hamsters, mice, rats) sex steroid–secreting neoplasms of the adrenal cortex develop. The genesis of these tumors may be prevented by the administration of sex hormone, either androgen or estrogen,[38] but not by cortisone.[39] When rats bearing such tumors were hypophysectomized, secretion of sex hormone by the neoplasms ceased.[40] Sex steroid secretion was resumed when gonadotrope was given, whereas ACTH was ineffective in stimulating the production of sex hormone.

Although in most inbred stocks of mice only adenomas develop, in ce mice carcinomas are the end result.[41] Approximately half the carcinomas of the adrenal cortex of ce mice exhibit hormone dependence, growing far better in castrates than in intact genetically compatible mice.[42]

It appears that genic factors operating in the adrenal cortex *per se* are responsible for the neoplastic alteration. When adrenals from tumor-susceptible and tumor-resistant parent stocks of mice were grafted into gonadectomized-adrenalectomized F_1 hybrids, cortical carcinomas developed in the adrenals of only the susceptible donor, indicating that tumor development is governed by the target tissue.[43]

Pituitary tumors composed of basophils have been described in association with adrenocortical tumors induced by gonadectomy.[44,45] Since estrogenic hormone may induce chromophobic pituitary adenomas,[46] and since pituitary tumors have appeared in association with radiation-induced and gonadotrophin-induced[47] ovarian tumors, the possibility of induction of pituitary tumors by estrogenic secretion of the peripheral tumors (ovarian and cortical) is a likelihood.[48]

When mice bearing postcastrational, estrogen-secreting adrenocortical adenomas were placed in parabiosis with immature intact females, the vaginal smears of the tumor-bearing females changed from estrus to anestrus, whereas the intact animals showed estrus smears resulting from ovarian stimulation.[49] Gonadotrophin was apparently preferentially utilized by the ovaries of the intact parabiont rather than by the cortical tumors of the castrated partner. When ACTH was administered to mice with cortical tumors their secretion of sex steroid was not stimulated, thus providing further evidence that these neoplasms are controlled by gonadotrophin.[50] Glucocorticoids as well as sex steroids have been obtained from castration-induced mouse adrenocortical tumors.[51] The basophilic adenomas of the mouse hypophysis occurring in conjunction with castration-induced adrenocortical tumors[44] might be analogous to Cushing's syndrome in man, in which pituitary basophilism is associated with increased secretion of adrenocortical glucocorticoids.

Pituitary Tumors. An experiment of Bielschowsky[47] is especially interesting in relation to

the development of pituitary adenomas which secrete hormone acting directly on the mammary gland. When a castrated and an intact rat were placed in parabiosis, ovarian tumors appeared in the intact animal as a result of increased gonadotrophic stimulation. The relatively large amount of estrogen secreted by the ovaries did not cross the parabiotic barrier but acted upon the anterior pituitary of the intact rat to induce an adenoma. The mammary glands of both parabionts were hyperstimulated, although the reproductive tract of the castrate was atrophic. The mammotrophic (lactogenic ?) hormone secreted by the pituitary tumor crossed the parabiotic barrier to stimulate the mammary glands of the castrated animal. The pituitary tumor was largely chromophobic but contained acidophils which were considered to be the secreting cells. Hormone stimulating the mammary gland of the mouse was also elaborated by pituitary tumors arising in heavily radiated mice.[52]

Furth[53] has described an interesting series of pituitary tumors induced in mice by whole body radiation. Neoplasms secreting ACTH, somatotrophic and mammotrophic hormones have been studied by grafting experiments. Although the gonads were damaged to a greater degree than the adrenal cortex in certain animals, ACTH- rather than gonadotrope-secreting tumors of the pituitary were induced. If a "feedback" mechanism is involved in the production of all these experimental pituitary tumors, it is intriguing to speculate concerning the possible somatic-humoral influences involved in stimulating the production of growth hormone–secreting pituitary adenomas.

Relationship of Estrogenic Hormone to Carcinogenesis. Estrogenic hormone has been involved in the genesis of a variety of experimental neoplasms and it is the only one of the endocrine steroids to which carcinogenic activity can definitely be ascribed. The evidence for classifying the estrogens as carcinogens is as good as for carcinogenic hydrocarbons if consideration is restricted to experiments on mice.

Mammary Carcinoma. This tumor occurs spontaneously in females of various inbred stocks of mice. The administration of estrogenic hormone may induce the development of mammary cancer in males of the inbred strains in which a high incidence occurs spontaneously in females.[54,55] Males of a strain in which spontaneous mammary carcinoma develops manifest testicular interstitial cell changes usually associated with the injection of estrogen.[56]

A filterable agent is involved in the spontaneous development of mammary cancer in inbred high mammary cancer strains. Foster nursing of high cancer offspring by low tumor mothers deprives the young of the tumor-promoting agent in the breast milk.[57]

Estrogenic hormone induces mammary cancer in mice only if the mammary tumor milk agent is present. Injection of estrogenic hormone into mice of low tumor strains does not cause the appearance of mammary cancer.[58] If, however, the mammary tumor agent is supplied to certain low tumor strains, estrogenic hormone (either secreted by the ovary or injected) may then induce mammary tumors.[58] At least three known factors are involved in the genesis of mammary cancer of inbred mice, the mammary tumor milk agent, a hormonal influence and a genetic susceptibility to the action of the first two.[59] If mice with all of these known factors are limited in their intake of calories, the incidence of mammary cancer may be drastically reduced.[60]

It has been suggested that a major effect of caloric restriction is estrogen-deprivation, dietary pseudohypophysectomy being a consequence of the reduced intake of calories.[61] Significant inhibition of mammary tumor formation occurs, however, with degrees of caloric restriction that do not seriously alter mating and fertility.[62] If strains of mice with a high mammary tumor incidence were fed a low cystine diet, the incidence of mammary cancer was remarkably reduced; the administration of diethylstilbestrol raised the incidence appreciably.[63]

Genetic influence is concerned with the survival and propagation of the mammary tumor agent[64] and probably also determines the intrinsic reaction of the mammary tissue to tumor-inciting influences. Apparently tumors may result from an unusual response of target tissue to hormonal stimuli which may be quantitatively but not qualitatively abnormal.

Ovariectomy may depress the incidence of spontaneous mammary cancer of mice. Age at ovariectomy[65] and susceptibility of the adrenal cortex to postcastrational estrogen-secreting tumors[2] are factors which decide the effect of ovariectomy on the incidence of mammary cancer. If ovarian hormone is produced by the adrenal cortex subsequent to the removal of the gonads, ovariectomy may not remarkably re-

duce the incidence of mammary cancer in such strains of mice. In strains of mice in which estrogen-secreting adenomas do not develop postovariectomy, age of ovariectomy is significant. If gonadectomy is performed after the ovaries have functioned for several months, complete withdrawal of estrogenic hormone does not inhibit tumorigenesis, although the time of appearance of mammary cancer is delayed and the total incidence may be somewhat reduced.[42]

Although estrogenic hormone is apparently not carcinogenic for the mouse mammary gland in the absence of the mammary tumor agent, carcinogenic hydrocarbons induce mammary tumors in high tumor strains deprived of the mammary tumor milk agent by foster nursing.[66–68] Carcinogenic hydrocarbon–induced tumors appear only in females or in males which have received estrogenic hormone. Histologic dissimilarities which may reflect etiologic differences[69] exist between carcinogen-induced and spontaneous mammary tumors.

In the rat, estrogenic hormone may be carcinogenic for the mammary epithelium.[70] Since a filterable agent has not been demonstrated for mammary tumors of this species the action of estrogen may here be "direct." Although the term "estrogenic" has been used synonymously with "hormonal" influence, the latter term is considered by some to imply pituitary origin.

Hormones have been considered to a great extent by the experimentalist from the standpoint of initiation and absolute progression of neoplastic growth. The influence of hormones on the rate of tumor growth has been neglected. Since hormonal therapy of human metastatic cancer of the breast is a recognized palliative procedure, some means of assessing this type of therapy in the mouse or in another experimental animal should be sought.

Hormones apparently influence the rate of growth of certain mammary cancers in mice.[71] In C57.RIII F_1 hybrids tumor growth may be relatively rapid during pregnancy with tumor regression occurring after parturition. This indication of hormonal dependence was supported by transplantation studies.[72] Estrogenic hormone augmented the growth of certain of these hormonally dependent tumors which grew only in histocompatible females but not males.

Testicular Tumors. Interstitial cell tumors of a mouse testis can be induced by administration of estrogenic hormone.[73–76] It is suspected that the pituitary is altered by treatment with estrogen, perhaps being stimulated to secrete either lutenizing hormone or interstitial cell–stimulating hormone, which may be more directly tumor-provoking. Leydig cell tumors occur spontaneously[76] and alterations in the interstitial cells resembling those preliminary to tumor induction by estrogen have appeared in male mice in which mammary cancer develops.[56]

Testicular tumors of similar structure have been induced in the rat by the transplantation of fetal testis to the spleen of castrated animals.[77,78] Although this procedure results routinely in the development of tumors when ovaries are similarly transplanted, thus far transplantation to the spleen has not proved successful for inducing tumors of the mouse testis, even in strains susceptible to the induction of interstitial cell tumors by exogenous estrogenic hormone.[79]

Of particular interest is the hormonal dependence of at least certain of these induced interstitial cell neoplasms.[75] When tumor transplants were made to animals of the same inbred strain, growth did not occur in some cases unless the recipient was injected with estrogenic hormone. Such dependent tumors metastasize (and are relatively benign), an anomalous situation since metastasis is usually a primary indication of autonomy.

Genetic factors are important in determining the tumorigenic response of the testis to estrogen. The Strong A and Balb/c strains are susceptible to induction whereas in resistant strains only an occasional tumor appears following estrogen treatment. The histologic and cytologic changes preliminary to tumorigenesis occur in the resistant as well as the susceptible strains. If testis from the newborn is transplanted to castrated F_1 hybrids between susceptible and resistant strains, the transplanted testis becomes tumorous upon administration of estrogen only if the transplant is from the parent susceptible strain.[80] This demonstrates again that the site of gene action determining susceptibility is in the target tissue itself.

Uterine and Vaginal Tumors. Although sarcomas of the mouse uterus occur sporadically in inbred stocks, spontaneous carcinomas of the female reproductive tract are unusual. In one inbred stock, however, carcinoma of the uterus and vagina developed in twelve of fifty-six females. When this stock was crossed with another stock in which such neoplasms do not appear spontaneously, carcinoma of the cervix

or vagina developed in thirteen of thirty-five estrogen-treated females. Of eighty-two genetically similar F_1 hybrid controls none had such lesions although five had uterine fibromas.[81] In hybrids between two inbred strains which have no special sensitivity to the development of spontaneous malignancy of the reproductive tract cervical cancer developed in twenty-five of forty-four which were treated with high doses of estrogen.

An adenocarcinoma of the uterus appeared in a constant estrus rat, suggesting the role of endogenously produced estrogen in the etiology of cancer of the female reproductive tract.[82] A hormonal imbalance resulting in sustained estrus was induced by transplanting testis from the newborn into intact newborn rats.[83] The gonadotrophin produced by the anterior pituitary of recipients is predominantly follicle-stimulating hormone and the ovaries do not become luteinized. It has been suggested that cancer of the female reproductive tract occurs more frequently in women with estrogen-secreting ovarian neoplasms.[84]

Leiomyomas of the uterus and similar extra-uterine smooth muscle tumors have been induced in the guinea pig by administration of estrogen.[85] Androgenic hormone and progesterone inhibited such effects. In the hamster this inhibition was not observed when the hormones were given in similar proportions.

Leukemia. Leukemia may be induced in specific inbred strains of mice by carcinogenic chemicals, ionizing radiations or estrogenic hormone. That the first two groups of leukemogenic agents are active in this way might have been anticipated since mouse leukemia satisfies the characteristics of neoplasms and the effects of x-rays on the hemopoietic tissues have long been known. The influence of estrogens was unanticipated at the time of discovery and represented a finding incidental to investigations on the influence of estrogenic hormone upon the development of mammary and cervical tumors.[86]

Not all strains of inbred mice are susceptible to the leukemia-inciting action of estrogens. Thus genetic factors determining susceptibility within the species are involved. Since the synthetic as well as the naturally occurring estrogens are tumorigenic, the hormonal effect may be "physiologic" rather than related intimately to molecular configuration.

Not only may estrogenic hormone be leukemogenic but it may augment the leukemia-inciting potency of x-rays.[87] Androgenic hormone may nullify the leukemogenic activity of estrogens[88] and diminish the leukemogenic effects of x-rays[88] or methylcholanthrene.[89] Castration has increased susceptibility to the spontaneous disease[90] and the leukemia-promoting effects of methylcholanthrene.[89]

The incidence of leukemia is higher in females than males in genetically controlled mouse populations.[42,90,91] In the human population, however, leukemia occurs more frequently in males.[92] Lymphocytic leukemia is the predominant variety in the mouse; granulocytic leukemia is found more frequently in man than in mice. Upton and Furth[93] have found that in the case of radiation-induced granulocytic leukemia of mice, males are more susceptible than females whereas the converse is true for lymphocytic leukemia. Orchiectomy resulted in increased susceptibility to the induction of lymphocytic but not granulocytic leukemia.

As in the case of other leukemogenic agents (x-rays, methylcholanthrene) the thymus may be the primary sensitive locus for the action of estrogenic hormone.[87]

Adrenalectomy has been reported to increase susceptibility to the development of both spontaneous[94] and radiation-induced mouse leukemia.[95] Large doses of cortisone at periodic intervals remarkably delay the development of spontaneous,[96] radiation- and methylcholanthrene-induced[42] leukemia.

Hypothyroidism favored the development of leukemia in high leukemia inbred strains of mice, but this was interpreted as being due to the increased weight of the hypothyroid mice and not to a specific effect on the susceptible tissue.[98]

The incidence of radiation-induced leukemia may be reduced by partially shielding hemopoietic tissue during whole body radiation with x-rays. The administration of appropriate amounts of estrogenic hormone has overcome the protective effects of bone marrow shielding[99] but not of thymic shielding in C57BL mice.

The influence of steroids on mouse leukemogenesis may have some significance for human leukemia. In both species cortical hormone may affect multiplication of leukemic cells[100,101] and in the mouse under certain well defined conditions both cortical and sex steroids may remarkably influence leukemogenesis. Androgenic hormone and cortisone oppose leukemogenesis whereas estrogen favors the induction of mouse leukemia.

Pituitary Tumors (Those Induced by Estrogen). As already indicated, injection of estrogenic hormone results in the development of chromophobic pituitary adenomas in specific strains of mice.[46] The estrogenic secretion of ovarian[47] and adrenocortical tumors[44] might have been responsible for the development of pituitary adenomas in the rat and mouse, respectively.

Direct Tumorigenesis. In the case of estrogenic hormone[102] and also another steroid hormone, desoxycorticosterone,[103] sarcomas have appeared at the site of injection. Since the sesame oil used as a vehicle is mildly carcinogenic in mice, interpretation is difficult.

Renal Tumors. Cortical tumors of the kidneys have occurred in male but not in female hamsters treated with diethylstilbestrol.[104]

Hepatic Tumors. The incidence of primary hepatic neoplasms is higher in males of human[105] and mouse[106] populations in which the frequency of occurrence is higher than usually encountered. The occurrence of primary hepatomas was reduced by gonadectomizing male mice.[106] However, excessive quantities of either endogenous or exogenous estrogen or androgen potentiated hepatic carcinogenesis by acetylaminofluorene.[107] In rats fed this carcinogen no tumors occurred in the organs which were hyperplastic as a result of the action of sex steroids, although the hyperplastic but functionless thyroid of rats fed both acetylaminofluorene and thiouracil was responsive to tumor development. Thiouracil protected the liver of rats against the carcinogenic action of both 2-acetylaminofluorene and butter yellow.[35] The influence is due to either hypothyroidism or a direct action of thiouracil upon the mechanism of tumor development.

With relatively high doses of 3,4-benzpyrene, male and female mice exhibited the same incidence of subcutaneous tumors; with minimal doses, however, a sex difference in susceptibility was noted, males showing a higher incidence than females.[108] The acceleration or inhibition of chemical carcinogenesis by sex hormones may be demonstrated or obscured depending on the dose of carcinogen, low enough in one case or too high in the other.

Adrenocortical and Pituitary Growth Hormones in Relation to Neoplasia. The influence of the adrenal cortex on initiation of carcinogenesis and the rate of tumor growth varies with the neoplasm. Glucocorticoids inhibit normal lymphopoiesis[109] and have a restraining influence on the growth of leukemic lymphocytes.[110] Adrenalectomy favors spontaneous[94] and radiation-induced[95] leukemogenesis and cortisone inhibits the development of spontaneous,[96] radiation-[97] and carcinogen-induced[42] leukemia. The first observed effect of cortisone on a neoplasm was the induced regression of a transplanted lymphosarcoma.[100] The effect of cortisone on certain non-lymphomatous transplanted tumors is similar to that observed for the lymphomas.[111] On the other hand, the Walker tumor grew at a reduced rate in adrenalectomized rats.[112]

Cortisone apparently accelerates methylcholanthrene-induced skin carcinogenesis[113] and favors the development of metastases in the case of certain transplanted and induced mouse tumors.[114,115] This effect of metastasis has been observed following stimulation of the human adrenal cortex with ACTH.[116] The primary growth of a transplanted tumor has been inhibited with the simultaneous induction of metastases.[114,117] When transplanted to normal mice the metastases behaved as the original tumor. Cortisone might cause cellular emboli to seed and grow as metastases.

By reducing the host immune response to foreign tissue, prior treatment with cortisone has favored growth of homologous[118] and heterologous[119] grafts. Apparently natural resistance to grafting is more easily overcome than an acquired immune state.[118]

Pituitary Growth Hormone. This hormone has been associated with the development of ovarian,[120] adrenal medullary[121] and lymphoid[122] tumors of rats. The tumorigenic effect of injected growth hormone was reduced if the animals were hypophysectomized, indicating that the pituitary gland *per se* was implicated. The carcinogenic effects of methylcholanthrene[123] and butter yellow[124] were remarkably reduced by hypophysectomy. Administration of growth hormone to mice bearing a transplantable mammary carcinoma resulted in an increase in the weight of both tumor and host.[124] In all hypophysectomy experiments the influence of inanition[62] must be differentiated from the effects of hormone withdrawal.

The recent observations on the course of human mammary cancer following hypophysectomy[125] have stimulated interest in the relationship of the pituitary gland to neoplastic growth. If palliation by hypophysectomy is demonstrable in ovariectomized-adrenalectomized subjects, an effect can be considered primarily one of withdrawal of a specific pituitary factor.

Hormone Dependence. Autonomy of neoplasms implies that they are not influenced by physiologic factors to the extent that progression in growth may be permanently interrupted. Encouraging is the evidence for at least partial dependence of some experimental neoplasms upon the hormones involved in their production. It appears that the hormonal inhibitors may also be factors in the continuing growth of cancers.

Some examples of hormone dependence of mouse tumors are the following: Estrogen-induced testicular tumors may frequently be transplantable only into estrogen-prepared mice[75] which are suitable for transplantation in all other respects (for example, genetic histocompatibility). Prostatic tumors of the mouse induced by methylcholanthrene may grow better upon transplantation into castrated rather than intact males, with androgen augmenting and estrogen inhibiting growth.[126] Pituitary tumors which secrete thyroid-stimulating hormone and are induced by hormonal imbalance will grow initially only in an athyroid host.[7] Certain castration-induced adrenocortical tumors in mice grow much better if transplanted into castrated rather than intact hosts of similar genetic constitution.[42] Ovarian tumors may be initially transplantable if grafted into the spleens of hosts which must be not only genetically compatible but also castrated.[15]

Of special significance is the observation of Foulds that some transplantable and spontaneous mammary carcinomas of mice are estrogen-dependent.[71,72] The fact that many transplanted carcinomas of the mammary gland may grow equally well in males and females had led to the generally accepted opinion that the established neoplasm is never dependent.

Genetic Factors: Site of Gene Action. Certain inbred strains of mice are susceptible and others resistant to the hormonal induction of specific tumors. Susceptibility is apparently inherited as a dominant factor, F_1 hybrids between susceptible and resistant strains demonstrating the same susceptibility as the parent strain which responds to hormonal imbalance by tumor development.

When gonadectomized-adrenalectomized F_1 hybrids between susceptible and resistant parent stocks received adrenal grafts from both, castration-induced cortical carcinomas developed only in the adrenal grafts supplied by the susceptible donors.[93] Since the same trophic hormonal stimulus acted upon both adrenals in the common host, the adrenal itself determined tumorigenesis. Similarly when grafts of testis were made into estrogen-treated F_1 hybrids between susceptible and resistant strains, tumors developed only in the grafts derived from the susceptible strain.[80] This phenomenon of control of tumorigenesis by the target tissue applies to pulmonary[127] and thymic tissue of mice[128] and will probably be found to be true generally.

Genetic or constitutional susceptibility to tumor development is thus a matter of tissue response of certain hosts to influences which may be innocuous to other individuals. On the other hand, certain agents (for example, carcinogenic hydrocarbons) appear to be universally carcinogenic for a species such as the mouse or rat; however, on closer scrutiny it is found that there are degrees of genetically determined susceptibility.

Relation of Viruses and Carcinogens to the Hormonal Induction of Neoplasms. Hormonal imbalance *per se* may experimentally result in the development of neoplasms. It has been demonstrated that multiple factors are intimately involved in tumorigenesis but that if certain ones are extremely potent, tumors may develop in the absence of others which are ordinarily necessary. Thus the development of certain animal neoplasms by hormonal factors mat be an exaggeration of one influence which in other cases may be contributory and not primary.

Tumors of the thyroid gland were induced by administration of thiouracil but the incidence was greatly increased if the rats were given a chemical carcinogen, acetylaminofluorene, in addition to thiouracil.[34,35] In C57BL mice, estrogenic hormone is not greatly leukemogenic independently but it increases the leukemogenic potency of x-rays.[99] Estrogenic hormone may, however, by itself induce leukemia under other genetic circumstances.[86] In the rat, mammary cancer has appeared in estrogen-treated animals.[70] There is no evidence that in this species a mammary tumor milk agent is concerned in mammary tumorigenesis and this could represent an instance of carcinogenesis with estrogenic hormone a "direct" cancer-producing agent.

Mammary carcinogenesis in the mouse is dependent upon estrogenic stimulation of the breast whether the neoplasm be incited by virus or carcinogen. That viruses may mediate hormonal action is indicated by mammary tumorigenesis in mice, since estrogenic hormone is not

tumor-inciting in the absence of the milk agent. Carcinogenic hydrocarbons may, however, induce mammary tumors in mice which do not possess the milk agent and from those tumors the milk agent cannot be obtained.[42]

The involvement of a filterable agent in the hormonal induction of tumors of the breast suggests that in the case of other tumors, although hormonal imbalance *per se* appears to be tumor-inciting, an agent analogous to the mammary tumor milk agent may be a cofactor.

In the future perhaps animal experiment and the clinical study of neoplasia may be more closely correlated than in the past. It is encouraging that so many parallels exist. Progress might be more rapid in the hormonal control of certain neoplasms if suitable animal material were available for study. For example, the inhibiting effect of estrogenic hormone on human mammary cancer[129,130] in the metastatic phase of its growth, the inhibition affecting both the primary neoplasm and metastases, has not been demonstrated for any animal neoplasm of similar tissue origin. Nor has there been a demonstration of the effect of androgenic hormone on the rate of growth of established mammary cancer although administration of male sex hormone reduced the spontaneous incidence in mice.[131] If effective control of the course of naturally occurring (spontaneous) neoplasms in mice can be achieved, it is likely that the principles will be applicable to human cancer.

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Physiologic Effects of Androgens and Estrogens in Man*

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CANCER of the breast, the prostate, the uterine cervix and fundus are now all known to share in varying degrees the endocrine responses of normal tissues in these several sites. It is therefore of immediate pertinence to this symposium to review our knowledge of the various local and systemic effects of endogenous as well as administered gonadal steroids in man, with special emphasis on their role in the genesis and therapy of cancer.

It is of considerable interest that medical experience does not include a single case of primary malignancy of the breast occurring in a prepuberal patient. Moreover, no documented case of malignancy in the hormonally dependent organs has been recorded in patients with sexual precocity.[1,2] This suggests that these organs require prolonged endocrine conditioning of the type derived from adult humoral relationships to become the seat of a malignancy.

Certain clinical manifestations of carcinoma of the breast serve to emphasize the importance of these humoral factors. The incidence of cancer of the breast in the male is estimated to constitute only about one to two per cent of the total occurrence of this disease.[3] Detailed endocrinologic studies of male patients with cancer of the breast have revealed no distinct endocrinopathic pattern.[4] But the regression of such tumors following orchiectomy suggests a supportive endogenous gonadal factor presumably estrogenic in character.[5]

Gynecomastia in men is encountered much more commonly than cancer, but even crude estimates of its relative frequency are not available. However, in certain individuals presenting clinically as hypogonadal males with gynecomastia the determination of genetic sex by study of their chromosomal pattern has recently permitted their identification as genetic females.[6,7] Nevertheless gynecomastia is capable of developing in previously normal adolescent or adult males under the influence of both endogenous and exogenous estrogens. There is as yet no documented case of cancer of the breast arising in a case of pre-existing gynecomastia attributable to endogenous hormonal imbalance. Contrariwise, we now have repeated reports of carcinoma of the breast arising in men with prostatic cancer treated for prolonged periods of time with stilbestrol.[8,9,10,11,12] It is apparent that such a neoplastic response to exogenous estrogen is extremely rare in view of the large total number of estrogen-treated patients with prostatic carcinoma. This low incidence of carcinoma stands in striking contrast to the much greater frequency of gynecomastia in this group. This is variously estimated as occurring in from 20 to 40 per cent.[13] However, the short life expectancy of patients with advanced prostatic malignancy may drastically limit the period of estrogen exposure, thus permitting only short term observations in most cases. On the whole, it appears that gynecomastia is a readily obtainable response to both exogenous and endogenous estrogen in the male and that malignancy is also (rarely) seen associated with prolonged estrogenic stimulation.

The breast of the human female depends upon endogenous gonadal factors for puberal development and normal cyclic functional changes. This is apparent from the synchronism between development of the breast and development of the tissues of the genital tract prior to onset of menses. In girls with puberal failure various patterns of development of the breast are observed, depending on the basis for the abnormality. Thus in patients with ovarian hypoplasia associated with an infantile genital tract, development of the breast may be totally lacking or it may approach the normal state.[2,14,15] This wide range of variability may be rationalized in terms of a purely quantitative ovarian insufficiency of varying degree. It must also then

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be considered that in some individuals the threshold for development of the breast in response to endogenous gonadal factors is far below that required for growth of the uterus, vagina and external genitalia. This inference is supported by the practically invariable growth response of these latter tissues to additional hormone provided by replacement therapy.

In cases of puberal failure due to total absence of differentiated ovarian tissue, for example, ovarian agenesis, practically all patients show complete absence of development of the breast.[2,4,14,16] However, recent study of the chromosomal pattern of patients with this syndrome indicate that about two of three have a male nuclear pattern and must therefore be regarded as cases of "gonadal dysgenesis" rather than simply as deficient females.[17] Still, the remaining third of these patients have a female chromosomal pattern and presumably represent females lacking endogenous ovarian hormones. Although a considerable degree of development of the breast is almost invariably induced by estrogens in these "ovarian agenesis" patients, it seldom reaches a level comparable to that of the normal adult even after prolonged and intensive therapy.[2,4] This emphasizes the necessity for factors other than estrogen for full development of the breast in the human female. Moreover, no benign or malignant tumors of the breast have been observed in such cases even after as long as six years of continuous estrogen replacement therapy.[4,18]

Although these remarkable growth effects of exogenous estrogen are readily induced in the breast of the prepuberal female and the normal adult male, the effect of such hormonal administration on the fully developed breast of the adult female is much less marked. In women still in the menarche even large doses of estrogen given over prolonged periods elicit little gross evidence of stimulation except for increased turgidity and tenderness. Redness of the nipple and areolae may occur and, less commonly, some areolar pigmentation is noted. Softening of pre-existing nodularity of the breast tissue may also occur. On the whole, the effect is not striking and in many instances would be unnoticed in casual clinical or histologic observation.

Similarly, the normal contralateral breast of postmenopausal patients treated continuously for cancer of the breast with high dosages of estrogen for as long as two years show little gross effect other than the marked areolar pigmentation which is seen in about one third of the cases. It is difficult to reconcile this relative unresponsiveness of the normal breast of the menstruating as well as of the postmenopausal woman with the accounts of exacerbation of cancer of the breast in younger women and the observed regression of cancer of the breast in postmenopausal women following estrogen administration.[19] Huseby and Thomas[20] have described a variable degree of epithelial proliferation irregularly observed in the normal breast tissue of estrogen-treated postmenopausal women. They comment that such proliferative effects may even be found immediately adjacent to areas of regressing carcinoma.

The estrogen-induced areolar pigmentation in some instances becomes extremely marked. The mechanism of this effect remains an interesting challenge, particularly in view of Lerner's demonstration of increased pigmentation in human skin under the influence of the melanocyte-stimulating hormone secreted by the intermediate lobe of the pituitary.[21]

The administration of estrogen to women in the menarche promptly leads to unequivocal uterine and vaginal response. The uterus becomes enlarged and hyperemic. There is a thickening of the myometrium and endometrial proliferation with a high mitotic index is regularly observed. The vagina shows extensive cornification and the vaginal pH is depressed. The cervix exudes an increased amount of clear, tenacious mucus.

In the postmenopausal patient estrogen induces little and frequently no uterine enlargement. The myometrial and endometrial responses are very limited in about half the patients and entirely lacking in the remainder. This is manifested by the absence of either "break through" or withdrawal bleeding in from one-half to one-third of estrogen-treated postmenopausal patients.[19,4] The vaginal mucosa, however, remains quite responsive to estrogen stimulation. It will show increased cornification and vascularity practically in all cases, often relieving a pre-existing atrophic vaginitis.

Although the endometrial response to estrogen in the postmenopausal woman is limited in frequency and degree, the problem of a potential carcinogenic action on the endometrium arises. In our own experience and that of numerous other observers[19,29,4] endometrial carcinoma has not developed following extended periods of

intensive estrogenization in older women. Nevertheless, the histopathologic studies of Gusberg[30] and of Hertig and Sommers[31] on the proliferative effects of protracted estrogen therapy on the endometrium of younger women are quite suggestive of a possible cause and effect relationship. Accordingly, it becomes mandatory to rule out pre-existing fundal or cervical malignancy on clinical and cytologic grounds before initiating estrogen therapy and to repeat these examinations at regular intervals during therapy.

In about 30 per cent of postmenopausal women the supporting soft-tissue structures of the pelvic floor become unduly flaccid and relaxed during estrogen therapy.[19,4] This leads to clinical symptoms to be discussed elsewhere in this symposium. This phenomenon indicates that estrogens have a profound softening and stretching effect upon connective tissue structures of the genital tract. This is somewhat comparable to the more generalized connective tissue effects produced by corticoids in other parts of the body.

Toxic dermatitis in response to estrogens is rare but documented cases are at hand.[19,4] This indicates that estrogens may function (rarely) as sensitizing agents but more general allergic phenomena are not observed. The gastrointestinal reactions to estrogens of nausea, vomiting and diarrhea, which in some cases are associated with general malaise, muscular aches and low-grade fever, suggest possible allergic manifestations but the nature of these reactions requires further study.

Before entering upon a combined discussion of the more general metabolic effects of both estrogen and androgen let us first consider some of the local and general effects of the androgens.

Since orchiectomy leads so dramatically and so frequently to regression of prostatic carcinoma, it has been widely held that androgens play a dominant role in the pathogenesis of this disease. Nevertheless, prostatic carcinoma has not thus far been produced either clinically or experimentally by the administration of androgen. Occult prostatic carcinoma is estimated to occur in from 14 to 46 per cent of the older male population.[22] Records of pharmaceutical sales and current clinical practices both reflect a widespread use of androgens in men of this age group. Yet, no clearly documented case of prostatic cancer attributable to prior androgen therapy has been reported. Lesser et al.[22] found no cases of prostatic carcinoma in a group of 100 older men treated for prolonged periods with testosterone. Moreover, extended endocrinologic study of patients with prostatic carcinoma has yielded no specific evidence of altered steroid metabolism which may not also be seen in other debilitated patients of comparable age and clinical status. It has been reported that the patient with prostatic carcinoma metabolizes administered cortisone in such a distinctive way as to excrete a higher than normal proportion of the ingested dose as ketosteroid.[23] These studies have not yet been confirmed elsewhere and are at variance with our own data.[4]

For the present, it must be considered that a distinctive alteration in endocrinologic function characteristic of the patient with prostatic carcinoma has yet to be demonstrated. Moreover, not all patients with prostatic carcinoma are benefited by estrogens or orchiectomy.[13] Furthermore, exacerbation of the disease, as evidenced by elevation of serum acid phosphatase levels following the administration of androgen, occurs in only about half the patients so tested.[24] Accordingly, it seems appropriate to consider that the remarkable therapeutic effects of estrogen administration and orchiectomy in prostatic cancer should not be characterized as "anti-androgenic" until these mechanisms are more completely understood.

The known effects of endogenous androgen in relation to reproductive function in man include (a) the development and maintenance of function and size of the prostate gland and seminal vesicles, and (b) the development and maintenance of such secondary sex characters as the voice, the beard and male hair distribution, the penis, and the secretory function of certain apocrine glands in the axilla and groin as well as the sebaceous apparatus of the skin and scalp.

The functional state of the seminal vesicles is reflected in the fructose content of the semen.[25] Similarly, the acid phosphatase content of the prostatic exprimate reflects the activity of the prostate.[26] It has been shown that the prostatic exprimate of the prepuberal male is low in acid phosphatase. The enzyme becomes elevated at puberty, remaining at a high level throughout the reproductive period and slowly receding to the prepuberal level during the later decades.[26] It is pertinent that this latter age period is associated with the maximum occurrence of prostatic cancer notwithstanding this and other manifestations of declining androgen production.

The plasma level of acid phosphatase is known to be elevated only in patients with prostatic carcinoma. Fishman et al.[27] have contributed greatly to the biochemical differentiation of "prostatic acid phosphatase" from acid phosphatase enzymes of more general origin in human plasma. The level of plasma prostatic phosphatase is widely accepted as a quantitative index of the metabolic activity of prostatic carcinoma in certain cases. The factors favoring the release of so large a molecule as this enzyme into the peripheral circulation are not understood. Nevertheless, clinical correlations permit acceptance of the acid phosphatase titer as a prognostic and analytic tool. In the dog viable ectopic prostatic grafts of which the intrinsic acid phosphatase content was raised to extremely high levels by the administration of androgen failed to raise the plasma level of the enzyme.[28] Thus some factor other than high ectopic tissue content is apparently involved in the production of hyperphosphatasemia. In addition, gross observation at necropsy clearly demonstrates that the level of antemortem hyperphosphatasemia is not correlated with the total bulk of carcinomatous tissue present. Patients with limited amounts of carcinomatous tissue may show enormous elevations of titer and others with massive osseous involvement may show completely normal titers. These discrepancies suggest that many factors such as production of enzymes, turn-over and permeability of tissue demand further study.

Two of the most disagreeable effects of androgen therapy in women, namely acne and hirsutism, are seen in 30 to 50 per cent of the cases. The physiologic basis for these effects had been previously considered to be the direct trophic action of androgen on the sebaceous glands and the hair follicles.[32] This conclusion was based largely on experimental studies in animals.[33] Extension of these studies has more recently demonstrated that anterior pituitary extracts are capable of restoring the atrophic sebaceous apparatus of the hypophysectomized rat without associated effects upon the gonads, adrenals or thyroid.[34] The demonstration of the activity of a specific pituitary trophic factor for the sebaceous apparatus in man would have great significance for our understanding of these undesirable effects of androgen therapy. In this connection it would also be pertinent to recall that the mammary gland itself is a specialized skin appendage whose response to androgens may be materially affected by the action of this newest of the pituitary trophic factors. Further elaboration of these studies will be anticipated with great interest.

Both acne and hirsutism are subject to extreme individual variation in women treated with androgen. Although no specific data are at hand, one gains the impression that both of these reactions decline in frequency and severity with advancing age. Some individuals are extremely responsive to as little as 25 mg. of testosterone propionate weekly; others will tolerate as much as 100 mg. three times weekly for periods of four to six months without evidence of acne or hirsutism. Pre-existing hirsutism does not appear to affect the degree of response obtained in any given individual. This wide variability in response renders the use of induced hirsutism as an index of the comparative androgenicity of a given steroid preparation quite difficult.

The larynx may be regarded as a secondary sex organ in that it attains its characteristically larger mass in the male under the influence of endogenous androgen. This sex difference is also reflected in the disparity in the incidence of cancer of the larynx between the sexes, some series indicating a ratio of sixteen males to one female with this disease.[35] It is not unexpected then that the administration of androgen will alter the larynx both structurally and functionally in women and in hypogonadal men. The laryngeal cartilages become heavier and clinically the thyroid cartilage becomes more prominent. The extrinsic muscles assume a greater mass, but little gross effect on the vocal chords is appreciated by laryngoscopic examination. The voice becomes at first coarse and then harsh. These voice changes, like hirsutism, are subject to wide individual variation and these two effects are usually seen in the same individuals.

The erythropoietic function is closely tied to basic sexual attributes. This is immediately apparent from the normally higher total erythrocyte count in males than in females. This sex difference in red count in the birds is readily reversed by the administration of androgen to the female or estrogen to the male.[36] In the mammal, erythropoiesis can be augmented by the administration of androgen but the depressant effect of estrogen is not readily demonstrable.[37] Clinical observation of such hormonal effects upon erythropoiesis is complicated by

numerous intervening factors also affecting the hematologic status of the patient. These include (a) the arrest of hemorrhage from extensively ulcerating lesions which may have been the basis for chronic blood loss; (b) improvement in food intake including iron and protein; and (c) the clearing of secondary infections in necrotizing lesions which begin to undergo regression. Hence markedly favorable but indirect hematologic effects sometimes follow either estrogen or androgen therapy. Clearly distinguishable from these indirect effects is the decisive erythrocyte-stimulating effect of androgen. This is usually associated with a ruddy coloration of the face and neck. In some cases this effect proceeds to polycythemia of major degree.[38] This subsides when androgen is discontinued. It may be considered that this erythropoietic action of androgen is merely a part of its more general anabolic action but the effect is specific for only one element of the bone marrow, there being no indication of an effect on thrombocytes or white cells.

The gonads exert important effects upon other hormone-producing organs. Both androgen and estrogen depress the urinary excretion and presumably the production of pituitary gonadotropin.[39] If this effect is sustained there follow varying degrees of atrophy of the gonads. In the elderly male given estrogen for prostatic carcinoma the initial histologic picture of the testis will range from that of a normal, functioning adult testis to that of profound senile atrophy. Hence it becomes very difficult to assess the true effects of the administration of estrogen on the human testis.[40] In younger men the administration of androgen clearly suppresses spermatogenic function[41] but little is known of the effect upon endogenous hormone production because of the peripheral effects of the administered androgen on the androgen-sensitive tissues. Conversely, however, Maddock et al.[42] have demonstrated that the human testis will increase not only its output of androgen but also of estrogen under the influence of chorionic gonadotropin. The administration of androgen to young women suppresses menses quite effectively and this is presumed to result from pituitary gonadotropic inhibition, although detailed data concerning the histologic features of such ovarian suppression are not available.

Experimental studies would lead one to expect that prolonged administration of estrogen could produce marked pituitary enlargement and pituitary tumors similar to those observed in the rat.[43] In our experience the pituitaries of male and female patients treated with stilbestrol for six months to two years show no gross alterations. This difference is all the more striking in view of the increased susceptibility of older rats to such estrogen-induced tumor formation.[44]

Similarly, rodents show a marked enlargement of the adrenal glands following either acute or chronic administration of estrogen. Necropsy data in our own laboratory show that the adrenals of patients dying during the course of brief or prolonged estrogen therapy are of normal weight and size when not involved with metastatic disease. We have made similar observations in conjunction with surgical adrenalectomy in previously estrogenized patients. This is of practical importance in evaluating proprietary claims regarding the clinical superiority of certain synthetic estrogens which are distinguished by their failure to cause adrenal enlargement in the rat.

Engstrom et al.[45] have demonstrated a rise in the protein-bound iodine fraction of the serum of both men and women given estrogens. This elevation is sustained during treatment and subsides when the medication is stopped. We have confirmed these observations and find that the estrogen-induced elevation in serum protein-bound iodine is not accompanied by clinical or laboratory evidence of increased thyroid function as manifested by basal metabolic rate, thyroidal uptake of radioactive iodine and pulse rate. This effect is therefore to be regarded as an augmentation of the iodine-binding capacity of the serum, an interpretation which is compatible with the studies of Dowling et al.[46] on similar effects in pregnancy.

Along similar lines, it has been recently shown that both estrogens and androgens exert profound effects upon the nature and composition of the plasma proteins.[47–50] In normal young females the alpha-lipoprotein fraction is higher in proportion to the beta-lipoprotein fraction than in normal males. This difference is not present in menopausal women. Under special clinical circumstances these relationships can be clearly but not completely reversed. No studies of the potential relationship of these effects on hormone-induced regressions of cancer of the breast or prostate have as yet been made.

The complex relationships of the gonadal hormones to the metabolism of calcium and of

other mineral substances are to be taken up in Dr. Baker's contribution to this symposium and will not be discussed here.

Our final consideration is concerned with the general effects of the androgens and estrogens upon the formation of protoplasm in extragenital foci. Since the pioneer studies of the protein anabolic action of androgens in the dog by Kochakian[51] and in man by Kenyon et al.,[52,53] little has been added. Space does not permit any exhaustive review of the abundant confirmatory and qualifying studies in this field. Briefly summarized, the metabolic actions of the androgens include: (a) nitrogen retention as manifested by reduced urinary excretion but without material change in fecal nitrogen; and (b) retention of sodium and potassium in amounts exceeding those accountable for by the nitrogen retained, and accompanied by normal plasma levels and compensatory water retention. Effects on nitrogen and potassium are less readily demonstrable with estrogens than with androgens but sodium and water retention are highly reproduceable effects. Comprehensive reviews of the clinical and experimental work in this general field are available.[54,55]

However, certain aspects are of particular interest to those concerned with steroid therapy in the patient with cancer. We must appreciate that whatever metabolic effects are obtained in an individual with progressive malignant disease are actually brought about against a countercurrent, as it were, of special influences imposed by the demands of the tumor. These include not only such obvious features as hemorrhage, infection and necrosis but also a myriad of more subtle factors such as the trapping of protein, iron and presumably other specific nutrillites in the tumor. Moreover, these influences are not in static balance but they fluctuate widely even in the face of all feasible measures on the part of the investigator to "keep things constant." This dynamic state becomes further altered as a given steroid begins to exert its effects on tumor and host, and it remains a major challenge to the clinician to analyze realistically what is happening.

Much of what the clinician refers to as "subjective improvement" actually has little to do with the effects of a given medication on the process of the tumor. This is especially true in the case of the gonadal steroids which normally play such a major psychobiologic role. It is especially interesting that androgens enhance the sexual libido of both male and female patients of all ages. In some female subjects this effect is extreme. Although it was initially observed that this extreme response was usually seen in patients with marked clitoral hypertrophy, more recent experience indicates that these two effects need not be associated. In contrast, estrogens exert no apparent effect on the libido of older women, and in younger women the effect is equivocal at best. Segaloff[56] has appropriately emphasized the major role of suggestion in the psychotherapeutic results obtained even in women treated with estrogens for menopausal symptoms of insomnia, headache and irritability. However, impotence is a frequent complaint of the estrogen-treated male subject.

The subjective phase of the action of the gonadal steroids is frequently manifested by increased appetite for food but craving for specific or bizarre foods has not been reported. These psychobiologic phenomena are mentioned mainly to emphasize the serious limitations in our knowledge of the mechanisms involved. Recent emphasis on the role of the hypothalamus in mediating such responses in experimental animals suggests its possible role in the observed clinical effects.

We have covered a wide variety of functional and morphologic effects of the gonadal steroids in man and have touched upon almost every phase of the body's economy. This clearly reflects the far-reaching metabolic consequences of the highly evolved pattern whereby the viviparous, lactating mammalian organism reproduces its kind. Who can tell which of these intriguing phenomena may yet provide a clue to the basic mechanism of steroid action in the palliation of cancer?

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Metabolism of Androgens, Estrogens and Corticoids*

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THE development of efficient chromatographic methods for the separation of steroids coupled with the availability of precise methods for the identification of minute amounts of these compounds, such as infrared analysis, have been important factors in the dramatic advances in our understanding of steroid metabolism. No less important perhaps was the application of organ perfusion and enzyme methods. This review will summarize briefly our present knowledge of steroid metabolism and deal with certain special problems of importance in cancer research and therapy. Detailed reviews of various aspects of steroid metabolism have been presented.[1-6]

BIOSYNTHESIS

Role of Acetate and Cholesterol. Steroid hormones have their origin in acetate and cholesterol. Both *in vivo* and *in vitro* technics support the idea that steroid hormones may be derived from these precursors but it is still unclear whether or not cholesterol is a necessary intermediate in the biosynthetic pathways. The biosynthetic pathway of acetate to cholesterol is known with reasonable certainty.[7,8] All the carbons of cholesterol may be derived from acetate and the most likely pathway is indicated by the reactions illustrated in Figures 1 and 2. Figure 1 details the suggested reaction sequence from acetate to squalene and Figure 2 indicates some of the possible intermediates between squalene and cholesterol.[9-11]

That cholesterol is a precursor of steroid hormones comes from a variety of experiments employing isotopes. In earlier experiments cholesterol was labeled with deuterium or isotopic carbon and the singly labeled steroid hormones or their metabolites were isolated. In these experiments there is indeed a strong likelihood that the transformation is truly direct but there always remains the possibility that the labeled cholesterol may be degraded to smaller units which in turn are converted to the hormone. This difficulty could be circumvented by using doubly labeled cholesterol and showing that the ratio of the two isotopes is the same in both the substrate (cholesterol) and the product (corticoids and androgens). Such experiments were reported by Werbin and LeRoy[12,13] who isolated doubly labeled tetrahydrocortisone, tetrahydrocortisol and 17-ketosteroids (including androsterone, etiocholanolone and 11-ketoetiocholanolone) after the administration of tritium- and C^{14}-labeled cholesterol. Other experiments, highly suggestive of cholesterol conversion to steroid hormones without preliminary breakdown of the cholesterol, include those discussed in detail elsewhere.[3,4]

FORMATION OF CORTICOIDS

Cortisol and Corticosterone. The adrenocortical pathway of cholesterol to pregnenolone to progesterone to cortisol and corticosterone is well established by methods employing perfusion studies, adrenal slices and homogenates as well as partially purified adrenal tissue enzyme preparations. Reference is made to the extensive reviews by Hechter and Pincus[4] and by Dorfman and Ungar[3] which document the many individual papers dealing with the subject. The biosynthetic reactions between cholesterol and acetate on the one hand and corticosterone and cortisol on the other are detailed in Figure 3. Pregnenolone, formed most likely from cholesterol, is oxidized to progesterone. Modifications of progesterone at carbon atoms 11, 17 and 21 are of an oxidative type involving molecular oxygen.[1] Evidence for the presence of all six theoretic intermediates between progesterone and cortisol is at hand either from direct isolation from adrenal tissue, direct formation from known adrenal steroids or

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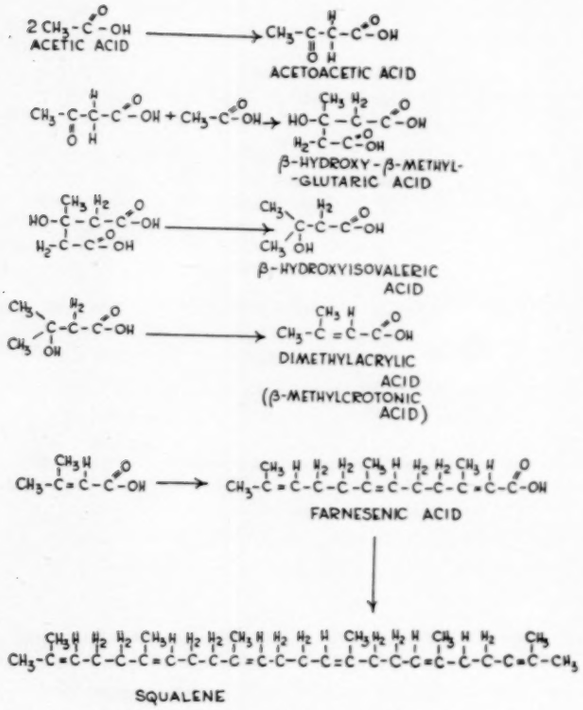


FIG. 1. Biosynthesis of squalene from acetate.

indirectly from isolation as urinary metabolites in man.

Aldosterone. The control of the biosynthesis of aldosterone differs from that of cortisol and corticosterone in that the former compound is not under direct control of ACTH and that the synthesis of this compound appears to depend at least in part on the concentration of blood sodium and potassium.[14] Administration of purified preparations of ACTH do not usually cause changes in aldosterone output. Hypophysectomized dogs continue to secrete high levels of the hormone.[15] Pituitary suppression in dogs by adequate doses of cortisol produced a marked decrease in cortisol and corticosterone secretion but did not influence the aldosterone secretion.[16] Recent studies indicate that although aldosterone is independent of ACTH the secretion of this hormone is dependent upon a neural or neurohumoral mechanism residing in the brain. This was demonstrated in the dog by employing a surgically decapitated animal the blood pressure of which was maintained by continuous infusion of norepinephrine and artificial respiration.[17]

Direct biosynthesis of aldosterone has been demonstrated by the direct conversion of desoxycorticosterone-21-C^{14} to aldosterone-21-C^{14}.[18] Indirect studies have shown that this mineralocorticoid can arise from progesterone.[19] This study, however, is at variance with that of Kahnt et al.[18] since desoxycorticosterone did not increase the aldosterone content of the perfusate. Corticosterone does not appear to be an efficient direct intermediate on the basis of two independent studies.

On the basis of available evidence the possible pathways of aldosterone are represented in Figure 4. Two unique reactions are required for the biosynthesis of aldosterone, the hydroxylation of carbon 18 and the oxidation of this group to the aldehyde. The hydroxylation reaction has been demonstrated in adrenal tissue using desoxycorticosterone as the substrate.[20] Since corticosterone does not appear to be an efficient substrate it is quite likely that the 18-hydroxylase is effective only in the absence of an 11β-hydroxy group and that may mean that 18-hydroxylation proceeds before 11β-hydroxylation in the biosynthesis of aldosterone.

FORMATION OF ANDROGENS

Adrenal Biosynthesis. The formation of adrenal androgens may proceed by way of direct biosynthetic pathways without involving C_{21} intermediates such as pregnenolone and progesterone or indirectly by means of the C_{21} steroids.

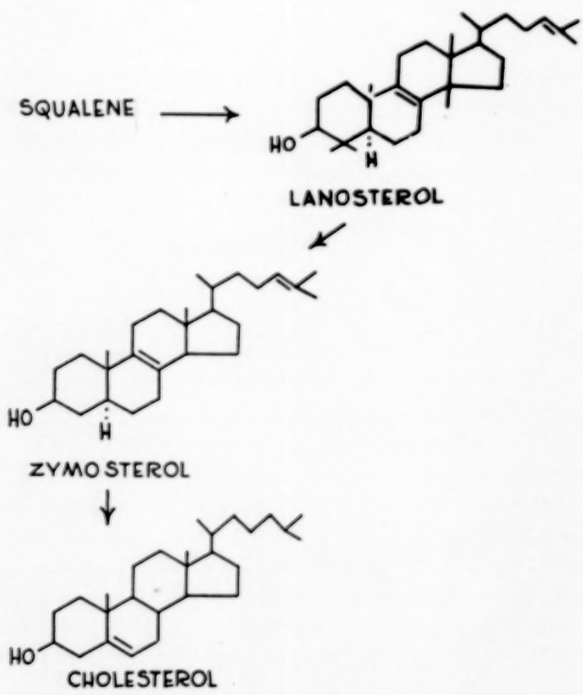


FIG. 2. Biosynthesis of cholesterol from squalene.

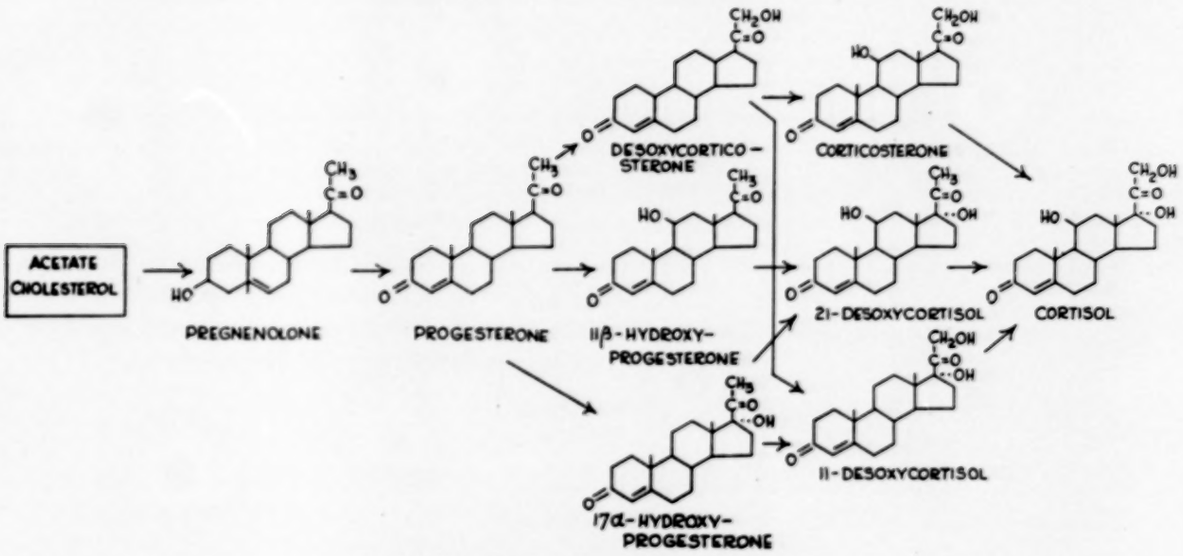


FIG. 3. Biosynthesis of cortisol and corticosterone.

(Fig. 5.) No definitive statement can be made as to whether or not both of these pathways are operative. The pathway by means of C_{21} intermediates has been demonstrated[21] by the incubation of progesterone-4-C^{14} with adrenal tissue followed by the isolation of newly formed Δ^4-androstene-3,17-dione-C^{14}, and by the perfusion of progesterone-4-C^{14} through bovine adrenals[22] and isolation of 11β-hydroxy-Δ^4-androstene-3,17-dione-C^{14}.

Adrenal tissue incubated with acetate-1-C^{14} yields labeled 17-ketosteroids.[23] These experiments do not exclude the possibility that 17-ketosteroids may be formed indirectly from C_{21} steroids. The isolation of dehydroepiandrosterone-C^{14} after the incubation of acetate-1-C^{14} strongly indicates that the former steroid is produced without a C_{21} intermediate. Since neither pregnenolone nor 17-hydroxypregnenolone has been converted to dehydroepiandrosterone and since steroids possessing the Δ^4-3-keto grouping are not converted to the Δ^5-3β-hydroxy steroids the appearance of dehydroepiandrosterone is suggestive evidence for a direct adrenal pathway to androgens.

Further evidence consistent with an independent pathway of androgen production is the appearance of androgens in human fetal adrenals before the appearance of significant amounts of corticoids;[24] the massive production of C_{19} steroids in patients with adrenal cancer showing only modest increments in C_{21} steroid production; the presence of massive amounts of cortisol in some patients with Cushing's disease without a concomitant increase in C_{19} steroids, and conditions of stress in which the corticoids are distinctly elevated while the 17-ketosteroids are decreased.[25]

Testicular Androgens. A pathway for the biosynthesis of androgens by rat and human testis has been established. (Fig. 6.) The pathway is similar to that found in the adrenal and consists in the formation of the androgens Δ^4-androstene-3, 17-dione and testosterone by way of pregnenolone, progesterone and 17α-hydroxyprogesterone.[26–28]

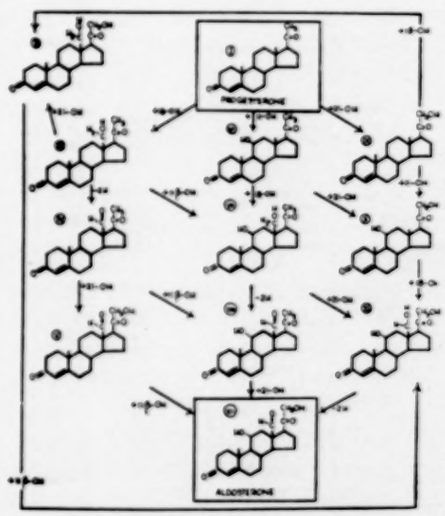


FIG. 4. Possible routes for the biosynthesis of aldosterone from progesterone.

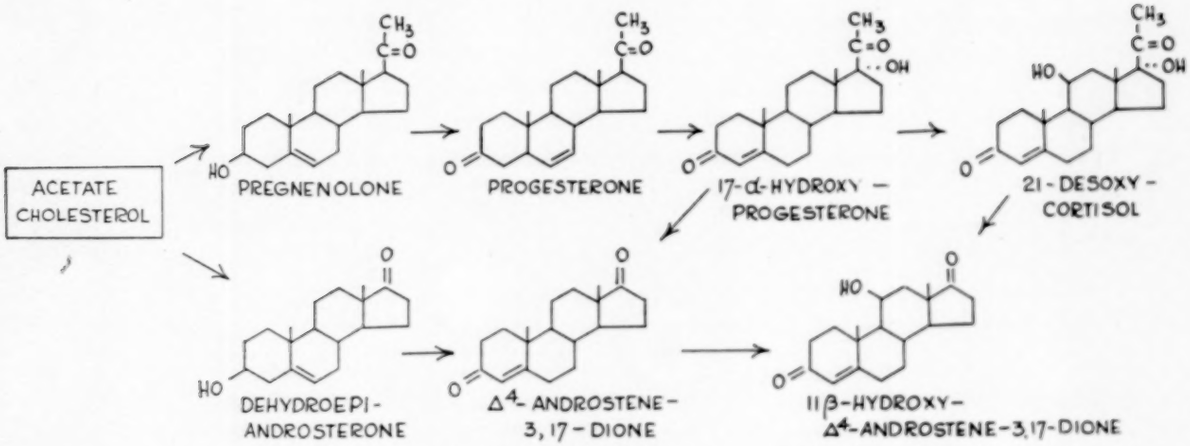


FIG. 5. Biosynthesis of adrenal androgens.

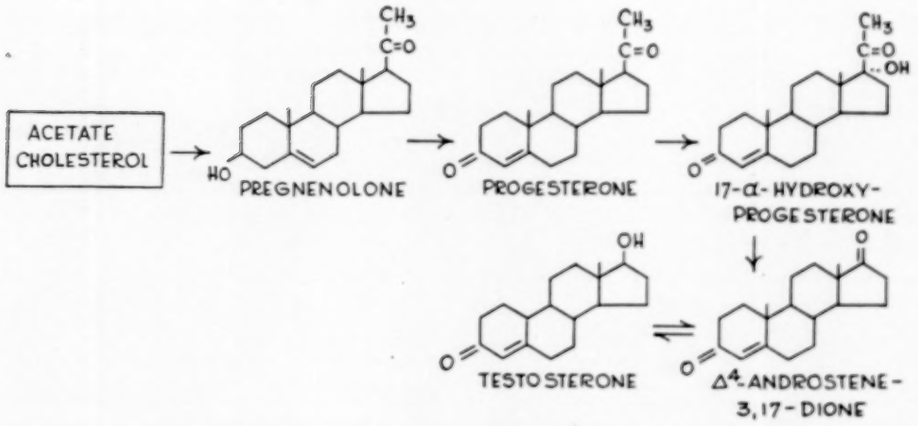


FIG. 6. Biosynthesis of androgens by the testis.

FORMATION OF ESTROGENS

The conversion of androgens to estrogens has been clearly demonstrated and may well be the principal biosynthetic route for estrogen production. This reaction was established by three independent studies. Incubation of human ovarian and stallion testicular tissue with testosterone-4-C^{14} resulted in the formation[29] of estradiol-17β-C^{14}. Intravenous administration[30] of the same labeled androgen to a pregnant mare resulted in the formation of estrone-C^{14}. In a third study, the direct conversion of Δ^4-androstene-3,17-dione-C^{14} to estrogen was demonstrated in various tissues including ovary, placenta and the adrenal.[31]

The key to the mechanism of this conversion lay in Meyer's study[31] which demonstrated that 19-hydroxy-Δ^4-androstene-3,17-dione (a naturally occurring steroid) was converted to estrogens, and that this hydroxylated intermediate and Δ^4-androstene-3,17-dione were more efficient substrates than 19-nortestosterone and $\Delta^{1,4}$-androstadien-3,17-dione. It is these facts that prompt the possible mechanism depicted in Figure 7. At least one additional reaction is needed as a route to the production of the aromatic ring A and therefore of an estrogen. The demonstration of the presence of naturally occurring 2α[32,33] and 2β[34] derivatives of the steroids could supply this needed reaction, and it is suggested that the estrogens are formed by the loss of the elements of water forming a Δ^1 double bond plus the loss of carbon 19 by way of the 19-hydroxy derivative.

Although a single mechanism for the formation of estrogens would make for simplicity, present evidence could be interpreted as indicating a second pathway. When acetate-1-C^{14} was administered to a pregnant mare the estrogens

isolated from the urine indicated that the molar specific activity of estrone was almost twice that of equilin and equilenin isolated from the same urine sample.[35] This difference appears to be highly significant and indicates that these two steroids are not related to estrone in a simple manner. When estrone-16-C^{14} was administered to a pregnant mare the isolated equilin and equilenin were not labeled.[35] This fact indicates that the ring B unsaturated estrogens are not derived from estrone, a view previously held by some as a logical possibility of estrogen metabolism. On the basis of these data it is suggested that the ring B unsaturated steroids are derived from an ethyltoluene residue (probably derived from the diet) plus two isoprenoid units (C_{10}) as illustrated in Figure 8. This is admittedly a hypothesis in need of testing but does have the value that it immediately suggests new experiments and may explain older isolated facts.

After condensation of the ethyltoluene unit with the C_{10} isoprenoid residue a C_{19} steroid would be formed. The angular methyl group at carbon 14 could be removed by the same reactions which remove this group from lanosterol; forming a C_{18} steroid. Hydroxylation reactions at carbons 3 and 17 would yield dihydroequilenin which is a naturally occurring steroid. Incomplete hydroxylation, that is, at position 17 only, could yield 3-desoxyequilenin which has also been isolated from natural sources. Reduction of ring B in dihydroequilenin would in this system yield in turn dihydroequilin and estradiol-17β. This therefore could be considered to be a possible alternative pathway for the biosynthesis of estradiol-17β and estrone.

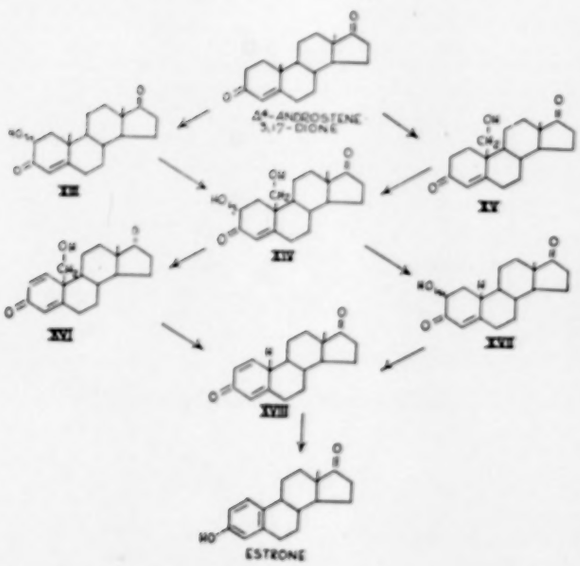


FIG. 7. Possible routes of biosynthesis of estrogens from androgens.

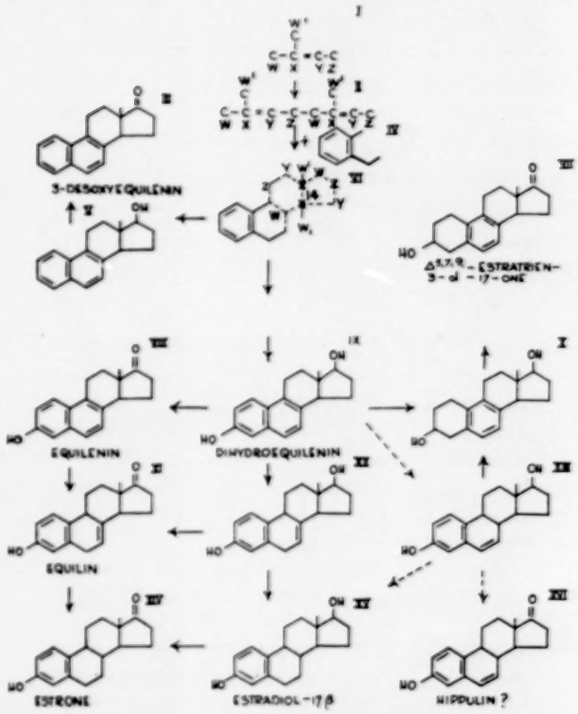


FIG. 8. Possible biosynthetic pathway for the formation of equilenin, equilin, estrone and estradiol-17β.

Since $\Delta^{5,7,9}$-estratrien-3-ol-17-one has been isolated from urine in which equilenin is present in high concentrations it is likely that the two steroids are related and that the ring A saturated steroid arises from dihydroequilenin.

The reactions depicted in Figure 8 are of interest in view of the possibility that some of the highly unsaturated steroids or related substances may play roles in the induction or maintenance of certain human tumors. Until recently there was little interest in these possible reactions since the ring B unsaturated compounds had not been found in human tissues. The presence of equilenin in human tissue has now been demonstrated by the isolation of this estrogen from adrenal cancer tissue.[36]

CATABOLIC REACTION

Rather than give in detail the individual catabolic reactions of steroids an attempt will be made to reconstruct the over-all reaction from the available *in vitro* and *in vivo* studies, emphasis being directed to what happens in man. Cata-

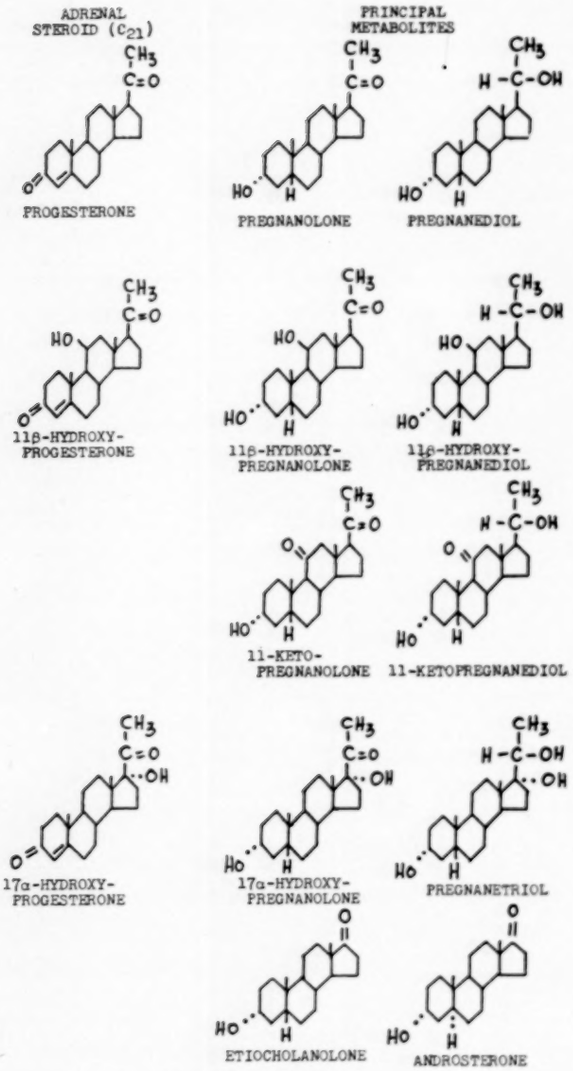


FIG. 9A. Metabolism of C_{21} steroids.

bolic reactions are those which modify the structure of the secreted hormones so that the biologic activity may be decreased, increased or changed from one class of material to another. In addition to these reactions, which are of the oxidative and reductive types, sulfate and glucuronic acid derivatives are known to be formed but will not be reviewed here. These have been discussed in detail elsewhere.[3]

Figures 9, 10, 11 summarize the steroids isolated from various steroid producing tissues, and their metabolites. The metabolites are principally those which occur in urine. Figure 9A through E, is concerned with neutral steroids possessing 21 carbon atoms. All these steroids possess a Δ^4-3-ketone group in ring A which in metabolism undergoes reduction of the Δ^4-double bond and the 3-ketone group. Although four stereoisomeric forms are possible, one stereoisomer is predominantly formed, the 3α, 5β form. Examples include the reduction of progesterone to pregnanediol and pregnanolone, and 17α-hydroxyprogesterone to 17α-hydroxypregnanolone and pregnanetriol. Those C_{21} steroids which possess oxygen functions at carbon atoms 17 and 20, such as 17α-hydroxyprogesterone and cortisol, undergo reactions involving loss of the sidechain to form 17-ketosteroids. 17α-Hydroxyprogesterone is converted to androsterone and etiocholanolone while cortisol is converted to four different 11-oxygenated 17-ketosteroids including 11β-hydroxyandrosterone, 11-ketoandrosterone, 11β-hydroxyetiocholanolone and 11-ketoetiocholanolone.

Dehydroepiandrosterone and testosterone are

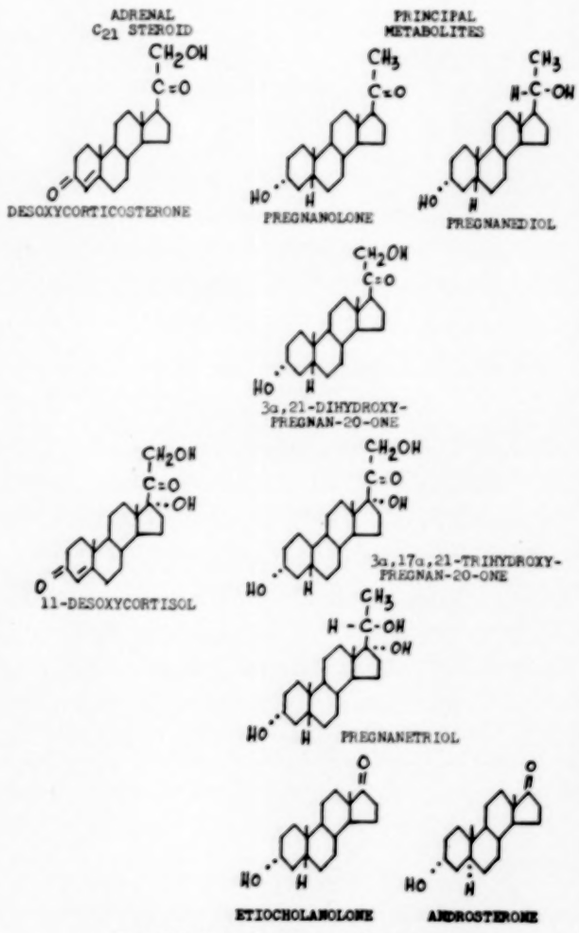


FIG. 9B. Metabolism of C_{21} steroids.

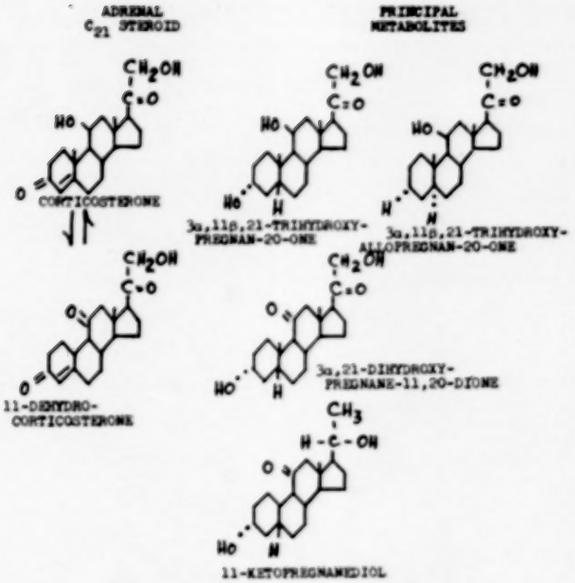


FIG. 9C. Metabolism of C_{21} steroids.

converted to Δ^4-androstene-3,17-dione which in turn is converted to androsterone and etiocholanolone in approximately a one to one proportion. The adrenal androgens, 11β-hydroxy-Δ^4-androstene-3,17-dione and adrenosterone, are similarly reduced to the four 11-oxygenated 17-ketosteroids, as indicated in Figure 10.

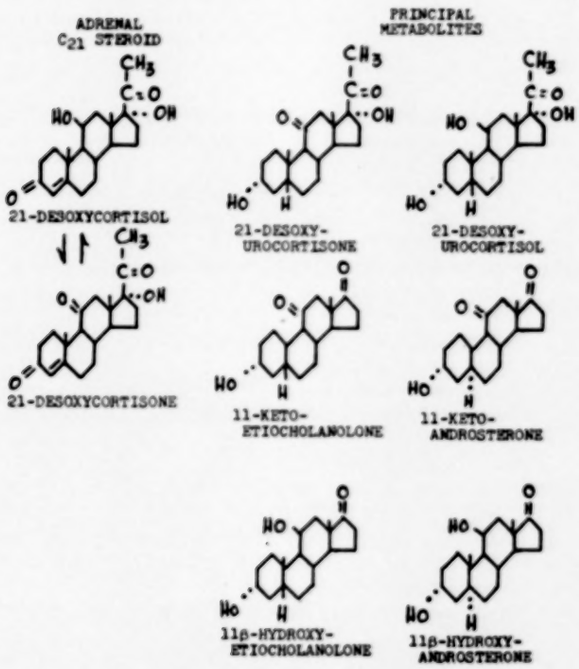


FIG. 9D. Metabolism of C_{21} steroids.

The estrogens, estradiol-17β and estrone, are interconvertible in metabolism and may give rise to estriol, estradiol-17α, and probably epiestriol. (Fig. 11.)

Interconvertibility of Steroids and Cancer Therapy. Steroid hormone therapy is known to be of value in cancer of the breast and prostate. Yet this value is limited both as to the percentage of patients showing objective improvement and the time during which the therapy is effective. In

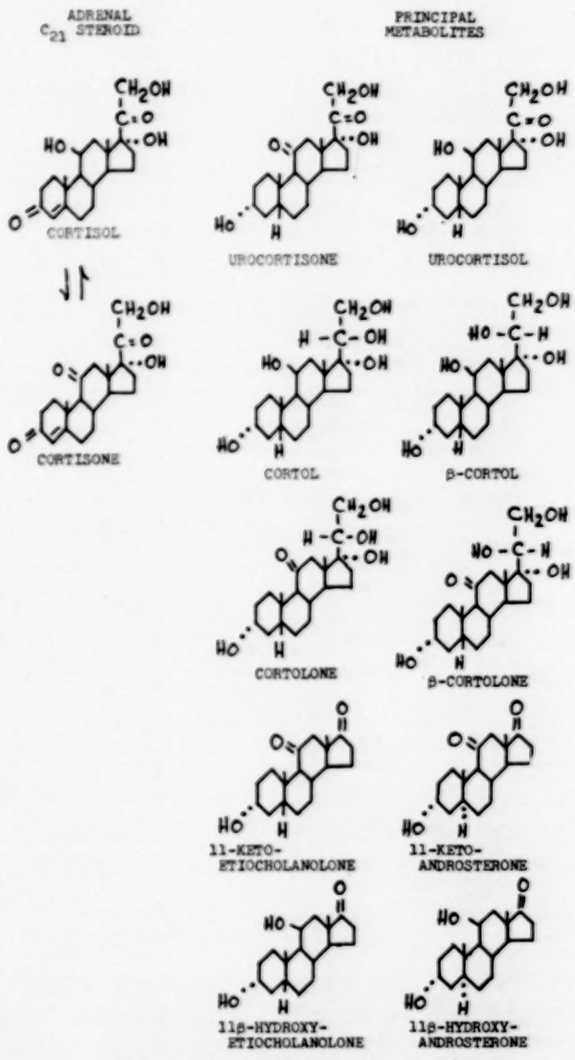


FIG. 9E. Metabolism of C_{21} steroids.

the case of cancer of the breast, estrogen therapy, although beneficial in postmenopausal patients, is known to accelerate the disease in premenopausal patients. Androgens appear to be the hormone of choice in premenopausal patients. With the definitive demonstration that testos-

terone can be converted to estrogens, the question is immediately asked whether or not the estrogen so produced after androgen therapy may not in part limit the therapeutic effectiveness of the hormone in premenopausal patients. This means that it is necessary to find steroids possessing anti-cancer (breast) activity and which are not metabolized to estrogens.

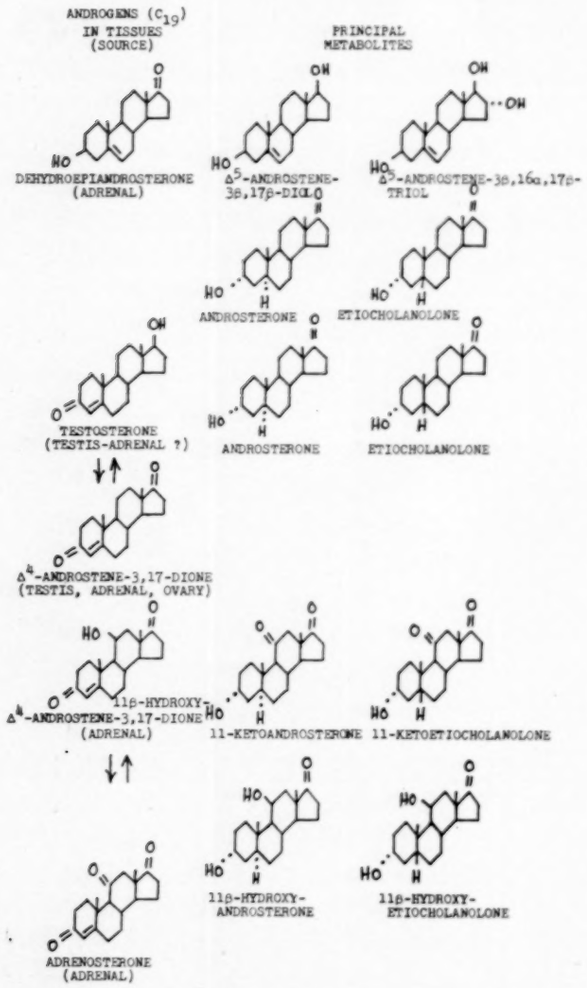


FIG. 10. Metabolism of C_{19} steroids.

It is generally agreed that removal of endogenous androgens from the circulation is a rational treatment for prostatic cancer. To this end castration and castration plus adrenalectomy have been practiced. When adrenalectomy is performed cortisone or cortisol is employed as substitution therapy. These steroids, although effective life maintenance drugs, have the disadvantage that they are metabolized in part to androgens. Thus, at least part of the advantages of adrenalectomy may be lost by

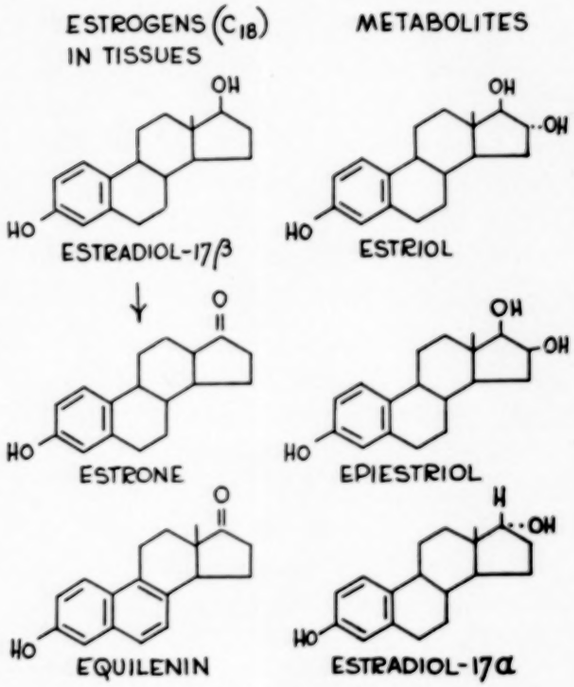


FIG. 11. Metabolism of estrogens.

substitution therapy. There is a need for corticoids which can maintain the adrenalectomized patient without being metabolized to androgens.

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Hormonal Modification in the Treatment of Disseminated Cancer of the Breast*

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METASTATIC cancer of the breast terminates in death but, even with inadequate or no treatment, survival may be several years. It is the duty of the attending physician to guide the course of the disease in such a way that the life of the patient may be as comfortable and useful as possible. Unfortunately many physicians feel so frustrated in the management of this disease that they practically abandon the patient, relying entirely on narcotics for palliation although they may skillfully treat other diseases in which survival may be expected to be much shorter.

It is established that temporary but gratifying palliation may be accomplished by hormone therapy and/or endocrine ablative procedures in certain patients with metastatic cancer of the breast but it is obvious to those working extensively in the field that there are many misconceptions as to the type of therapy, the proper timing and the dose schedule. As a result, many patients are not obtaining the benefit possible. It is as deplorable for a physician to treat a patient with metastatic cancer of the breast with inadequate or poorly selected hormone therapy as it is for the surgeon to do incomplete surgery for the same disease or the radiotherapist to misuse radiation therapy.

During the last decade numerous papers have been written on the effect of steroid hormone alteration in disseminated cancer of the breast,[1–5] but because of the marked variability in the course of the disease and the lack of definitive criteria for evaluation of the results there have been great differences in the reported palliative effects. Many questions will remain unanswered until a better means of selecting patients and a definitive measurement of tumor regression can be established. We will, nevertheless, present our impressions as to the proper indications, order of therapy and benefit that one may expect, using as our criteria of objective tumor regression decrease in size of dominant malignant neoplastic lesions without the simultaneous development of new lesions or progression of other established lesions. We do not consider improved calcium balance or the so called "phosphatase flare" as evidence of objective regression when not accompanied by the criteria specified.

Indications for Steroidal Alteration in the Treatment of Metastatic Cancer of the Breast. All forms of steroidal therapy and endocrine ablative procedures are at best of only temporary benefit and are of necessity always associated with mild or profound endocrinologic alteration. The course of metastatic cancer of the breast is extremely variable, progressing rapidly or remaining static for years. It is therefore important that steroidal alteration be used only in the treatment of patients showing actively progressing disease, and be withheld from patients with clinically isolated metastatic lesions that may better be treated by other means, and withheld also from those in whom the disease is remaining static. Longer palliation may be obtained by withholding steroidal alterations until the disease becomes so disseminated that adequate control is impossible with standard forms of therapy. On the other hand, withholding steroidal therapy until the patient is in a hopeless state is to be condemned. The timing of each step of therapy is of the utmost importance. It is necessary to appreciate the limitations of steroidal therapy as well as the possible palliative effects in order to give the patient maximal benefit.

ESTROGEN THERAPY

Although the use of estrogen seems irrational from the point of view of experimentation in animals and to those who hold the view that cancer of the breast is "estrogen-dependent" in about 50 per cent of cases, some of the most gratifying and prolonged regressions occur with this steroid. The mechanism is unknown al-

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though some investigators attempt to explain it on the basis of anterior pituitary suppression rather than on the basis of direct action of estrogen at the cell level.

Indications. Estrogens should be selected whenever steroid therapy is indicated for the first trial of steroid therapy for disseminated cancer of the breast in all patients five or more years following the menopause, with the exception of those patients who have previously shown definite evidence of tumor suppression by removal of the ovaries and those showing evidence of estrogen activity by clinical and laboratory criteria. Estrogen therapy has the advantage of producing less hormonal distortion to the patient than do any of the other endocrine procedures used in the treatment of cancer of the female breast. Estrogens are indicated also in cancer of the male breast irrespective of the age of the individual.

Beneficial Effects Produced by Estrogens. One of three patients five years after the menopause may be expected to achieve temporary suppression of the tumor by the use of pharmacologic doses of estrogen. As the interval between the menopause and the time of starting therapy becomes longer, the percentage of patients responding favorably increases. At least 50 per cent of patients seventy years or older may be expected to show tumor regression. Regression will vary from a very temporary decrease in the size of the tumor metastases to major regression. Patients responding favorably will usually show tumor regression lasting from six to fourteen months; occasionally, however, a patient will show tumor regression lasting for a period of four or five years. Soft tissue lesions seem to respond more favorably than do bone lesions although recalcification of osseous lesions occurs in about 25 per cent of those with skeletal metastases. Visceral lesions may also respond favorably, although extensive hepatic metastases seldom show beneficial response. Some long-standing lesions may regress while new lesions appear; under such circumstances, however, regression should not be ascribed to therapy as it also occurs at times in untreated patients.

Method of Administration. The most economical and convenient method of administration of estrogens is the oral use of diethylstilbestrol, 5 mg. three times a day, or ethinyl estradiol, 1 mg. three times a day. Although premarin® is considerably more expensive it has the advantage of producing less nausea than stilbestrol. Estradiol dipropionate or estradiol benzoate in sesame oil may be substituted for oral medication in doses of 5 mg. twice a week should parenteral estrogens be indicated. The drug should be continued at this dose level until it is definitely demonstrable that the tumor is progressing or unless untoward reactions develop.

Complications Associated with Estrogen Therapy. The most serious unfavorable reaction to estrogen therapy is augmentation of the tumor. As already mentioned, this occurs frequently in patients before or immediately after the menopause and is manifest by rapid growth of lesions and the appearance of new lesions. This must not be mistaken for the temporary flare that sometimes occurs with estrogen therapy during the first few days preceding regression. In patients with extensive osseous lesions hypercalcemia may develop which, if untreated, may be rapidly fatal. Nausea, usually the first symptom of hypercalcemia, should not be confused with the nausea produced by the administration of estrogen.

Patients of all ages with intact uteri will have uterine bleeding at some time during prolonged high dose estrogen therapy, generally on omitting one or more dose. This is at times controlled by temporarily doubling the dose of estrogen but it may be necessary to omit the drug until the bleeding stops. Omission of the drug is usually followed by a period of more profuse bleeding. If bleeding does not stop in five or six days, 100 mg. of progesterone in sesame oil should be given intramuscularly for three days. If this does not control the bleeding the patient should be examined for other causes of uterine hemorrhage.

The proestrogen tace® is converted in the gastrointestinal tract to physiologically active estrogen which is stored in the body fats and slowly excreted for many weeks. Since abrupt interruption of the administration of estrogen may be indicated, the use of this drug is not advised. For the same reason, long-acting estrogenic substances given intramuscularly should not be administered.

Estrogens may reactivate cystic disease of the breast which may be mistaken for a cancerous growth. They also produce relaxation of the pelvic floor which frequently causes incontinence, and increase in pre-existing cystocele, or prolapse uteri. An unusual complication that has occurred twice in my experience has been hematometria in aged patients with stenosis of the cervical os. Nausea associated with

oral medication is common but frequently is controlled by giving the medication on a full stomach, temporarily reducing the dose or changing to another estrogen preparation. We have found sodium estrone in its natural form (premarin®) to be tolerated at times when diethylstilbestrol is not. Nausea, common on first starting therapy, frequently disappears if the patient is encouraged to continue therapy. Increased pigmentation commonly seen in pregnancy occurs with continuous therapy; this is especially noted on the nipple where the pigmentation may become very marked and crusted. If this pigmentation of the nipple does not occur one becomes suspicious that the patient is not taking her full dose of estrogen. Uterine fibroids that have become atrophic after the menopause may become reactivated and grow to considerable size during estrogen therapy.

One of the actions of estrogen is the production of sodium retention. This may become marked in the aged patient with pre-existing cardiac or renal disease and may necessitate sodium restriction in order to avoid congestive heart failure.

ANDROGEN THERAPY

Androgen therapy, despite its popularity, is one of the least desirable forms of therapy for metastatic cancer of the breast because of the profound endocrine alterations produced in the female and because it is infrequently of benefit in producing tumor regression. Because of its anabolic effect patients very frequently feel stronger, have improved appetite and hemograms, and gain weight. Improvement in these respects must not, however, be interpreted as evidence of tumor regression.

The mechanism of androgen-produced regression is not established. It may be related to the suppressive action of the hormone on the anterior pituitary gland. Its blocking action on the production of estrogen cannot explain its relatively consistent action in both pre- and postmenopausal groups.

Indications. Androgen therapy should not be the first form of steroid alteration given to a patient with metastatic cancer of the breast. In the patient who is still a menstruant, androgens are indicated only following relapse or failure after removal of ovarian function either by adequate ovarian radiation or surgical removal of the ovaries. In the postmenopausal patient, androgens are indicated during relapse following the use of estrogens or if adequate therapy has failed to produce a favorable response.

Beneficial Effects Produced by Androgens. Tumor regression occurs with adequate androgen therapy in from 20 to 25 per cent of patients so treated both in the premenopausal and postmenopausal periods. Very few patients respond at the menopause or immediately following the menopause. Although recalcification of destructive osseous lesions occurs in only about 20 per cent of patients so afflicted, relief of bone pains occurs in up to 60 per cent of patients. The beneficial effect of this relief of pain is apt to be offset by the occurrence of pathologic fractures because of lack of true healing of the bone associated with this relief of pain. Patients frequently show a marked increase in appetite, weight gain and increased strength as well as improved hemogram, all of which may occur despite no evidence of tumor regression. Initially there may be increased pain from osseous metastases, or dramatic relief may occur. Neither of these symptoms should be construed as evidence of augmentation or regression of the malignant neoplasm and judgment of the efficacy of the therapy must await the appearance of objective changes. As with estrogens, no evidence of tumor regression may be demonstrable for the first two or three months after the initiation of therapy.

Method of Administration. As the tumor-suppressive action of androgens seems to depend upon the androgenicity of the drug,[6] the use of drugs with low androgenicity has no advantage over testosterone propionate. The recommended dose of testosterone propionate is 50 to 100 mg. in sesame oil given intramuscularly three times a week. As rapid withdrawal of therapy is indicated should unfavorable reactions occur, long-acting androgens are not recommended despite their convenience. Methyl testosterone may have a place in the therapy of cancer of the female breast but adequate data have not been accumulated to establish its usefulness, and it appears to be inferior in the treatment of metastases to bone. Androgen therapy should be continued as long as evidence of tumor suppression is demonstrable or as long as no evidence of tumor progression appears, unless its physiologic effects are untenable to the patient.

Complications Associated with the Use of Androgens. Although the purpose of androgen therapy in

carcinoma of the female breast is to produce temporary tumor regression this goal is achieved in only 20 to 25 per cent of patients. Enthusiasm for this slight degree of therapeutic effectiveness is diluted by the invariable development of virilization. The degree of virilization produced depends on the individual end-organ response. Hirsutism, hoarseness or deepening of the voice, acne, sexual eroticism, baldness, amenorrhea, muscular hypertrophy, weight gain, rounding and flushing of the facies and fat deposits on the shoulder and back of the neck, hypertension, tachycardia and nervousness vary with the individual patient. Acne is more common in those patients who had the condition in puberty or who have a family history of acne.

Androgens may produce profound changes in electrolyte metabolism. Sodium retention may cause congestive heart failure in a patient with pre-existing cardiac disease, increase in effusive processes and aggravation of pre-existing lymphedema of the arms. Finally, and by far the most serious complication of androgen therapy because it may prove fatal, is the development of hypercalcemia. This occurs more commonly during androgen than estrogen therapy.[7] Any one of these complications may necessarily require omission of the drug.

CORTISONE, HYDROCORTISONE, PREDNISONE AND PREDNISOLONE

Cortisone and hydrocortisone have been used in pharmacologic doses in attempts to produce tumor regression in cancer of the breast. It has been postulated that these drugs might produce sufficient suppression of the adrenal cortex to obtain the same beneficial effects as surgical ablation of the gland. Pearson[8] reports objective tumor regression in 50 per cent of patients treated with 200 mg. of cortisone a day; however the regression could be maintained for only two to three months despite continuous therapy. Segaloff[9] failed to obtain evidence of tumor regression with this therapy. In twenty[10] patients maintained on a regimen of 75 mg. of cortisone a day we observed tumor regression in three but two patients showed nearly complete replacement of the adrenals by metastatic disease. Recently we have followed twenty-seven patients maintained on 50 to 100 mg. of prednisolone and have been able to establish tumor regression by our criteria in only one, a patient in whom amenorrhea and hot flashes developed during therapy, suggesting the possibility that the regression was due to failure of ovarian function.[11] Lemon[12] feels that marked tumor suppression may be obtained with cortisone in patients previously oophorectomized but we have been unable to reproduce these results. All are agreed that this form of therapy does not reproduce the definitive regression observed in some patients following adrenalectomy-oophorectomy.

We reported several years ago suggestive evidence of augmented tumor spread in mammary cancer during corticotropin therapy[13] and Luft[14] has observed a similar effect of this hormone in hypophysectomized patients.

However, despite the fact that specific tumor suppression may not be produced, these drugs are frequently of great value in controlling certain complications of metastatic cancer of the breast as well as in producing temporary but gratifying palliation. It is of interest that this palliation may be produced in patients whose adrenals or pituitary have been removed as well as in those with these organs intact. Furthermore, the beneficial effects of these hormones frequently occur much more rapidly than could be expected on the basis of tumor suppression.

How these beneficial effects are produced by the adrenal cortical hormones and their analogues is not well understood. One action undoubtedly is that of blocking the normal tissue reaction against the foreign invasive process, thereby reducing edema, swelling and inflammatory cell infiltration.

Indications for Corticoid Therapy. Corticoid therapy is indicated whenever palliation is needed in patients of all ages and both sexes after it becomes obvious that specific tumor-suppressive agents are not producing adequate palliation. As these drugs produce many of the side effects of androgens, the two drugs should not be given together in large doses for any extended period. Corticoid therapy may be of value as the only form of treatment or in conjunction with other hormone therapy.

Specific corticoid therapy is indicated for hypercalcemia and for control of neurologic symptoms of cerebral metastases as well as for replacement therapy in the presence of adrenal insufficiency due to destruction of the adrenals by surgical ablation or tumor replacement of the glands. It is also specifically indicated as a bone marrow stimulant in myelophthisic anemia due to tumor invasion, radiation or chemotherapy. It is frequently the only satisfactory therapy for radiation pneumonitis.

Beneficial Effects of Therapy. Corticoids may relieve pain from osseous metastases, dyspnea from pulmonary metastases, discomfort from inflammatory reaction about the tumor site, anemia due to depressed bone marrow and pneumonitis following radiation therapy to the chest. Jaundice associated with hepatic metastases is at times relieved. Lymphedema of the arm and effusive processes are frequently relieved by prednisone or prednisolone whereas the natural hormones may worsen these conditions. One of the most interesting effects of corticoid therapy is the control of neurologic symptoms produced by cerebral metastases. Both motor and sensory paralysis may be rapidly ameliorated. Visual disturbances and convulsions may disappear within twenty-four hours after the start of intensive therapy. Hypercalcemia due to extensive osseous metastases is reduced in most cases with large doses of corticoids, usually more effectively than by the use of other measures such as sodium citrate or versene and without the possible danger of producing damage to the renal apparatus. Weight gain due to stimulation of appetite is common even in the presence of progression of the neoplastic growth.

Method of Administration. For general palliation 50 to 100 mg. of cortisone by the oral route in three or four divided doses a day is advised. Hydrocortisone is effective in slightly lower doses, and 20 to 50 mg. of prednisone or prednisolone is at least equally effective. The dose of any one of these drugs should be kept at the lowest level required for maximum palliation. As prednisone and prednisolone cause less sodium retention and potassium loss we feel they are preferable to the natural hormones, especially if large doses are indicated. For the treatment of severe neurologic manifestations produced by cerebral metastases we have found 100 to 200 mg. of prednisone or prednisolone over a twenty-four-hour period to be frequently extremely effective. Two hundred milligrams of hydrocortisone given by slow intravenous drip in 10 per cent glucose solution over a twenty-four-hour period is also often effective but the medication should be shifted to prednisone or prednisolone for maintenance therapy. The dose of prednisolone is gradually reduced to the lowest effective level. As the cerebral metastatic lesions gradually progress it may be necessary to increase the dose of these drugs to a higher level for adequate control of the symptoms. As it is probable that most of the beneficial effect of these drugs is due to the decrease in edema and inflammatory reaction about the tumor in the central nervous system we feel the corticoids with the least sodium-retaining action are preferable. In the treatment of hypercalcemia we have found 200 mg. of hydrocortisone or 100 mg. of prednisolone over a twenty-four-hour period by slow intravenous drip, to be effective in bringing the serum calcium down to normal. After the electrolyte disturbance has been corrected the dose of the drug should be gradually reduced or stopped, depending upon the course of the serum calcium level. Since all these drugs produce adrenal cortical suppression it is extremely important not to stop their use abruptly, especially if the patient is in a state of stress from the disease, as such omission of a drug may produce acute adrenal insufficiency.

Complications Associated with Therapy. All the complications of pharmacologic doses of corticoid therapy must be expected with prolonged administration of any of the corticoids. These include Cushing's syndrome, steroid diabetes, muscular wasting, masking of infections, peptic ulceration and emotional disturbances. The "moon facies," fat pads, hirsutism and acne are unpopular complications with the female. One should beware not to make the unfortunate patient more unhappy from the use of the hormone than from the symptoms of the malignant process. One must guard against hypertension, sodium retention and potassium deficit when using the natural hormones by limiting sodium intake and adding potassium to the diet. This is not usually a problem with the use of prednisone or prednisolone even with long-term, high-dose therapy. It is our impression that peptic ulceration occurs more frequently with the doses of prednisolone and prednisone we have employed than with similar patients given 75 mg. of cortisone a day. This may be due to the fact that the dose of prednisolone and prednisone is relatively higher. Because of this we usually give the patient a modified ulcer regimen if the medication is to be continued over any extended period of time. A serious complication associated with long-term use of prednisolone is the development of adrenal insufficiency even in the presence of continued administration of this drug. This is usually precipitated by an intercurrent infection or a down-hill course of the malignant disease.

GONADECTOMY AND RADIATION OF THE OVARIES

Obliteration of ovarian function has been used therapeutically in metastatic cancer of the breast since before the start of the 20th century. There have been waves of enthusiasm followed by periods when this therapy was practically abandoned. No accurate data on the effectiveness of this procedure have been obtained although several studies have been reported in recent years. As the only endocrine alteration produced by this procedure is the characteristic menopausal syndrome, and as the operation carries a relatively low morbidity, it is the least objectionable of all ablative procedures. It is impossible to compare the effectiveness of surgical versus radiation obliteration because of the marked variability of x-ray technics in various institutions. Surgical removal of the ovaries has the advantage of complete, abrupt removal of all ovarian estrogens whereas following radiation to the ovaries function may not be completely suppressed or complete suppression may not occur immediately. In metastatic cancer of the male breast orchiectomy in any age group is a valid procedure.

Treves[5] has recently reported tumor regression in metastatic cancer of the female breast in over 50 per cent of premenopausal women and an occasional favorable response in patients after the menopause. In our series of fifty cases, however, we have been able to demonstrate objective regression in only about 20 per cent of premenopausal women. These contradictory figures are probably due to differences in criteria of regression in the two institutions rather than the relative activity of the ovary in patients from New York and Chicago. It does not seem logical to expect more favorable regression following the removal of gonadal estrogens alone than following removal of both gonadal and cortical estrogens. What percentage of women actually respond to this form of therapy can be determined only after large series of oophorectomized patients have been accumulated. Evidences of tumor regression following surgical castration usually appear within six weeks following the procedure but may be manifest as early as the seventh postoperative day. Following x-ray castration the beneficial effects may not be demonstrable for three or four months. In cancer of the male breast a beneficial response following orchiectomy occurs in about 60 per cent of patients. In either sex, removal of gonadal sex steroids may produce tumor regression that lasts anywhere from six months to two or three years before reactivation is demonstrable.

As it has never been demonstrated that gonadectomy ever produces permanent tumor suppression, prophylactic gonadectomy does not seem a rational procedure and we believe that gonadectomy should be reserved for the time when palliation is indicated.

ADRENALECTOMY

It is definitely established that in certain cases of metastatic cancer of the breast tumor regression occurs following surgical removal of the adrenal glands in patients whose gonads have been removed or have ceased to have appreciable secretory function.[15–17] Tumor regression has been reported to occur in 35 to 50 per cent of patients who have been adrenalectomized. We have observed the effect of this procedure on sixty patients in a far-advanced state of disseminated disease. Objective regression was demonstrated in 36 per cent, but in only 26 per cent did we consider that adequate palliation and rehabilitation had been produced long enough to make this a useful procedure.[18] It is one thing to point proudly to evidence of tumor regression on the basis of decreased urinary calcium excretion, "phosphatase flare" or slight reduction in the size of one or two tumor sites but quite another to judge this regression as worthwhile to the subject. Because of the necessity for continuous experienced supervision of these patients for the rest of their lives, and in view of the small percentage of patients actually benefited, this procedure should be limited to a few highly selected patients. The greatest real contribution of adrenalectomy to the problem of cancer of the breast has been the demonstration that adrenal hormones influence the growth of this tumor.

Indications for Adrenalectomy. Adequate material has not been accumulated to establish definitely which patients may be expected to respond favorably to adrenalectomy but it appears that patients who have previously responded favorably to gonadectomy are more apt to have a regression following adrenalectomy. Jesseman has great confidence in the "estrogen sensitivity test" but Baker has not found this of value. We ourselves have had no experience with this test; however, we feel that short-term

administration of estrogen to a patient with cancer of the breast may have an entirely different effect from that obtained if the drug is used for a longer period.

Only those patients who show actively progressing disease that does not respond favorably to sex steroid therapy should be selected for this type of management. Patients who have previously responded favorably to estrogens usually will get no benefit from adrenalectomy. Most patients with extensive pulmonary or hepatic metastases are poor candidates for adrenalectomy whereas patients with extensive osseous disease and minimal visceral disease may be greatly benefited. Restricting this procedure to patients who are in the terminal state of the disease is as unjustified in our opinion, as adrenalectomizing patients who may be expected to respond favorably to less radical procedures. Only reliable and intelligent patients should be selected for adrenalectomy since the management of "surgical Addison's disease" requires intelligence on the part of the patient as well as skill on the part of the attending physician.

HYPOPHYSECTOMY

As with adrenalectomy, the important contribution of hypophysectomy in cancer of the breast has been the demonstration that certain tumors of the breast are influenced by the pituitary gland,[19,20] but whether this is through the medium of other glands of internal secretion or directly through the pituitary hormones is not yet established. We feel strongly that this is an experimental procedure fraught with great danger and that the palliation achieved, in relation to other less drastic forms of treatment, is undetermined. We are of the opinion that for the present hypophysectomy should be limited to few institutions for investigative purposes alone. It should not be presented to the patient or relative of the patient as an established form of therapy. Its value compared to adrenalectomy is not established.

SUGGESTED CHRONOLOGIC ORDER OF THERAPY IN PATIENTS WITH DISSEMINATED MAMMARY CANCER

Because of the marked variability of the disease no hard and fast rule can be laid down as to what particular form of therapy should be given at a particular time. However, I will attempt to outline the general plan of endocrine alteration that is usually of the greatest advantage in these patients.

For patients premenopausal or less than five years postmenopausal: The first form of endocrine alteration that should be used when the disease cannot be adequately controlled by local radiation or surgery is obliteration of ovarian function, preferably by surgery, unless the only clinical evidence of the disease is pleural effusion, in which case intracavitary nitrogen mustard or isotopic radiation is usually preferable. Ovarian ablation should then be delayed until further evidence of dissemination appears.

In cases in which the disease continues to progress after a period of two or three months and there is no clinical or laboratory evidence of estrogen activity, estrogens may be tried. This should be done cautiously as danger of augmenting the disease is great at this period. Should augmentation be demonstrated after two or three weeks the drug should immediately be omitted. If progression of the disease is obvious after two or three months of therapy one must then choose between producing virilism by the use of androgens or subject the patient to adrenalectomy with its objectionable features. If it is believed that the patient will not be made too miserable by the production of virilism, androgen should be tried. If androgen therapy proves to be of value it should be continued until progression of the disease is apparent. Omission of androgen is at times followed by tumor regression; it is therefore wise to observe the patient for at least one month without therapy. Should the disease still progress at this time one must choose between adrenal ablation, with the hope of producing tumor regression, or non-specific palliation with corticoids. If visceral disease is advanced, adrenalectomy is contraindicated.

If, following ovarian ablation the patient experiences gratifying results, a period of no therapy should follow until the disease is again reactivated, at which time androgen or adrenal ablation therapy should be chosen. It is possible that such a patient may have a better chance of obtaining regression of the tumor following adrenalectomy than the patient not responding favorably to oophorectomy. During the entire course of therapy it is wise not to multiply treatment upon treatment in such a way that one cannot judge what is or is not being accomplished, since selection of the succeeding courses of therapy may be made more intelligently if one knows how the patient has responded to

previous treatment. One must not, however, in one's enthusiasm to be "scientific" permit a weight-bearing bone to fracture from lack of local radiation.

In patients five or more years after the menopause: Estrogen therapy should be the initial form of hormonal alteration. The closer the patient is to the menopause the more closely should she be observed for evidence of tumor augmentation with estrogen therapy. On the other hand, the older the patient the greater the possibility for gratifying tumor regression.

Should estrogen therapy be of no value after a trial of two to three months androgen should be used after a period of observation without treatment. Aside from the complaint of eroticism, virilization does not seem to be as objectionable to the older age group as the younger, but hypertension and sodium retention may be more serious. Should androgen be contraindicated or should progression of the disease follow remission with androgen the only hope of further tumor control is adrenalectomy for those patients whose physical state is such that they may reasonably be expected to withstand the procedure. If adrenalectomy is deemed unwise, corticoids should be used for their palliative effect, not with the hope of actually producing tumor regression.

In the male patient with cancer of the breast: The first endocrine procedure should be castration if the patient can accept this psychologically. If not, estrogen therapy should be given. Should neither of these procedures be of benefit adrenalectomy is the only other present means of producing tumor regression. This procedure can also follow relapse following remission from estrogen or castration. Corticoids may be used for palliation together with other therapy or alone.

Despite some very gratifying regressions following hypophysectomy this procedure is not recommended for reasons mentioned herein. When further improvement in technic has been developed it may surplant gonadectomy, adrenalectomy and androgen therapy.

Metastatic Lesions Responding More Favorably to Procedures Other than Endocrine Alterations. Although metastases to weight-bearing bone may recalcify under endocrine therapy, recalcification usually occurs more rapidly and with less danger of fracture if the affected bone is radiated. Isolated lesions of the spine, pelvis or femur are best treated by the use of radiation alone or in conjunction with endocrine procedures if disseminated disease is also present. It is wise to choose radiation or surgery when regional glands or local recurrence at the operative site alone is present unless progression of the disease is very rapid. Large ulcerated areas may respond better to combine steroidal and radiation therapy. Massive effusive processes are more quickly controlled by intracavitary nitrogen mustard or appropriate radioactive isotopes than by hormone therapy. Needless to say, obstructive complications cannot be expected to respond adequately to management other than surgical. Only by the judicious use of all these palliative tools, together with the aid of neurosurgical procedures, analgesia and common sense psychotherapy, can the best palliation be obtained.

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Hormone Therapy in Prostatic Cancer*

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THE relatively common occurrence of prostatic cancer, the frequency with which it is inoperable, and the simplicity and success of palliative endocrine treatment combine to make the hormonal control of prostatic cancer a common and an important therapeutic experience. In order to indicate the place and justify the use of endocrine therapy in the management of the patient with prostatic cancer, consideration must be given to other aspects of the problem. Accordingly, some space will be devoted to the pathology, clinical classification, incidence, natural history and diagnosis of prostatic neoplasms before any discussion of therapy is attempted.

PATHOLOGY

The vast majority of prostatic cancers are carcinomas and most are adenocarcinomas. Although the common site of origin of prostatic cancers is in the peripheral portion of the gland (usually the lateral and posterior segments), a few neoplasms appear to originate within the adenomatous enlargements responsible for benign prostatic obstruction. These pathologic facts have several important clinical implications:

1. In addition to the morphologic resemblance of prostatic adenocarcinoma to the normal glandular elements of the prostate there is a physiologic similarity which forms the rational basis of endocrine therapy.

2. The occurrence of prostatic cancer in the posterior peripheral portion of the gland increases the prospects of clinical detection through digital rectal examination.

3. The occurrence of prostatic cancer in the peripheral portion of the gland indicates the general futility of methods of enucleation prostatectomy as a means for prophylaxis of the disease. (Fig. 1.) Smith and Woodruff[1] reported that 6 per cent of a series of 648 patients with carcinoma of the prostate had previously undergone subtotal prostatectomy for what appeared to be benign prostatic enlargement.

4. The long term survival of a patient in whom an apparently benign prostatic obstruction is treated by enucleation prostatectomy and in whom pathologic examination discloses carcinoma in the surgical specimen may result from the possibility that a small focus of prostatic cancer arising within such adenomatous hyperplasia is completely eliminated by the very procedure which led to its detection. Prostatic carcinoma is found in some 10 per cent of prostates enucleated for the relief of apparently benign obstructions.[1–3] Most cancers found in this way probably originate in peripheral portions of the prostate and merely invade the adenoma, but some undoubtedly originate within the adenoma *per se*.

CLINICAL CLASSIFICATION

For the purposes of this discussion it is convenient to divide prostatic cancers into four clinical stages:

Stage I, clinically latent prostatic cancer. This is a stage of the disease in which neither symptoms nor signs nor laboratory studies, short of actual pathologic examination, lead to suspicion of the presence of cancer but microscopic study of tissue from the prostate reveals the presence of previously unsuspected cancer.

Stage II, clinically manifest early prostatic cancer. This is a stage of the disease in which symptoms are absent but a suspicion of carcinoma is aroused by the presence on digital rectal examination of a more or less circumscribed area of induration apparently confined within the limits of the prostatic capsule and no evidence of metastasis can be found.

Stage III, clinically manifest locally advanced prostatic cancer without evidence of distant metastases. This is a stage of the disease in which local symptoms from the neoplasm are present to a variable degree and digital rectal examination discloses a variable degree of induration of the prostate, seminal vesicles and bladder

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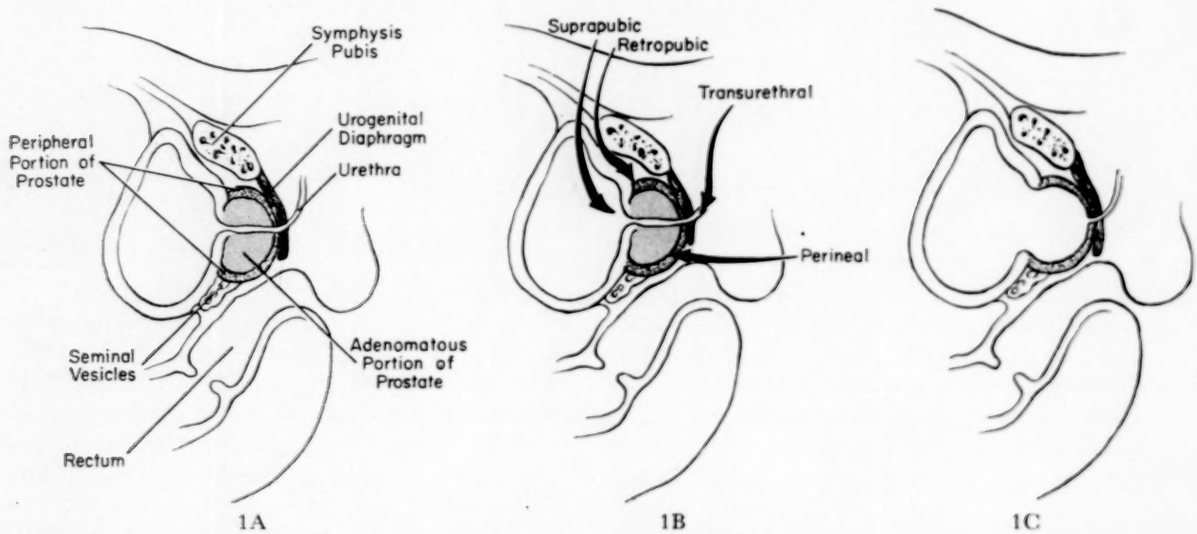


FIG. 1. A, diagrammatic sagittal section of pelvis to show relationships of prostate to adjacent structures. B, diagrammatic sagittal section of pelvis to show various surgical routes of "enucleation" prostatectomy. C, diagrammatic sagittal section of pelvis to show residual prostate after an ideal enucleation prostatectomy.

base, but evidence of metastases cannot be demonstrated.

Stage IV, clinically manifest advanced prostatic cancer with evidence of distant metastases. This is a stage of the disease in which the manifestations of the cancer in the prostatic area vary in respect to symptoms and digital rectal findings, but conclusive evidence of metastases is demonstrated.

With regard to this method of classification into stages it is important at the outset to point out the following facts: (1) The classification is arbitrary since the cancer process is a dynamic one whereas the stages, as defined, are static. (2) The classification is clinical rather than pathologic. The significance of this limitation is due to the fact that the pathologic stage of the disease may be very different from the clinical stage. Stage I cancers are not always small.[4] Stage II cancers are not always pathologically confined within the prostatic capsule. This is abundantly clear from the therapeutic failures following attempts at cure of stage II lesions with total excision by means of radical prostatectomy.[5] Experience with radical cystectomy and pelvic exenteration in an attempt at total excision of stage III lesions has indicated that metastases are almost invariably found at the time of laparotomy although they were not preoperatively demonstrable.[6] Stage IV lesions are not always locally advanced. Patients with "occult" prostatic cancers present with evidence of distant metastases at a time when the prostatic primary tumor is not clinically manifest.

Despite the obvious limitations of this arbitrary clinical classification, it is on the basis of available clinical information that therapeutic plans for the patient ordinarily are proposed; therefore use of this method of classification into stages can be defended, if not endorsed.

INCIDENCE

In considering the incidence of prostatic cancer it is necessary to distinguish between clinically manifest (stages II, III and IV) and clinically latent (stage I) neoplasms.

Clinically Manifest Prostatic Cancer (*Stages II, III and IV*). Prostatic cancer caused 13,218 deaths in the United States in 1954[7] and is the cause of death in about 5 per cent of men over fifty years of age.[8] In the interval 1947 to 1951, in Connecticut, the age-adjusted incidence rate of prostatic cancer ranged between 27.8 and 31.5 per 100,000 men.[9] Although the rising total of deaths from prostatic cancer reported each year is in part ascribable to an aging population, age-adjusted incidence rates suggest that there may be an increase in incidence as well.[9] The striking increase in incidence rates occurring with age is indicated in Table I.

Although an exact formulation of the relative incidence of stage II, III and IV neoplasms among patients with clinically manifest cancers is not possible from available data, a reasonable ap-

proximation is that 5 to 10 per cent are stage II lesions, 15 to 30 per cent are stage III lesions and 60 to 80 per cent are stage IV lesions.

Clinically Latent Prostatic Cancer (Stage I). Impressive as is the incidence of clinically manifest prostatic cancer, the incidence of latent prostatic cancer is even more striking. This is evident from three types of pathologic observations:

1. Pathologic study of prostatic tissue enucleated during operations for the relief of benign prostatic obstruction reveals a 10 per cent incidence of clinically latent cancer.[1–3] Since such enucleated prostatic specimens do not contain the most common sites of origin of prostatic cancer, for example, the peripheral portions of the gland, it is evident that 10 per cent is a conservative estimate for the incidence of prostatic cancer in individuals with apparently benign prostatic obstructions.

2. Efforts have been made to detect more clinically latent prostatic cancers by deliberate open biopsy of the posterior surface of the prostate. Hudson and coworkers,[4] dealing with a group of patients who had no or minimal urinary symptoms and variable degrees of abnormality of the prostate on digital rectal examination, found thirty-nine prostatic cancers in three hundred patients, an incidence of 13 per cent.

3. Pathologic study by step-section technic of the whole prostate in men of different age groups dying of causes other than prostatic cancer has revealed an amazingly high incidence of clinically latent prostatic cancer.[10–14] The incidence increases with age. (Table II.) In spite of the statistical limitations of such data it seems safe to say that the incidence of clinically latent prostatic cancer far exceeds that of clinically manifest cancer in all age groups studied.

TABLE I
INCIDENCE OF CLINICALLY MANIFEST PROSTATIC CANCER (STAGES II, III, IV)
Per 100,000 Males by Age*

Age Group (yr.)	Incidence
40–44	0.3
45–49	1.9
50–54	8.3
55–59	31.5
60–64	71.3
65–69	139.4
70–74	277.6
75–79	475.9
80–84	539.1
85 and over	732.4

* Taken from data compiled in "Cancer in Connecticut, 1935 to 1951."[9]

TABLE II
INCIDENCE RANGES* OF CLINICALLY LATENT PROSTATIC CANCER (STAGE I)
Per 100 Males by Age

Age Group (yr.)	Incidence Range
30–39	4
40–49	4.9–8.7–8.7–17
50–59	5.3–9.7–10.4–14
60–69	17.8–17.9–18.5–23
70–79	21–25–28.3–31.8
80–89	17.6–29–38.7–48.5
90–99	80

* The incidence ranges were calculated from the data of the following authors: Andrews;[14] Edwards et al.;[12] Gaynor;[10] Hirst and Bergman;[11] Moore.[13] Since the number of patients studied were relatively small, some of the incidence values are not statistically significant.

NATURAL HISTORY

For present purposes the natural history of prostatic cancer may be defined as the clinical and pathologic manifestations of the untreated disease projected upon a time scale. No natural history of cancer in human beings has been satisfactorily documented and cancer of the prostate is no exception. However, the limited information available is essential to an understanding of current philosophies of treatment and will be separately defined, but only in its temporal aspects, for each of the four clinical stages.

Stage I. Even granting the assumption that the clinically latent prostatic cancer will, in time, invariably become a clinically manifest lesion, how much time is required and what other factors are involved? Although it is a reasonable guess that endocrine factors are somehow concerned, there is no convincing evidence that such is the case and, interestingly enough, there is no evidence that administration of testosterone has "activated" any latent prostatic cancers.[15] With regard to the time between the onset of a latent prostatic cancer and the appearance of a clinically manifest lesion, information is scanty and of debatable significance.

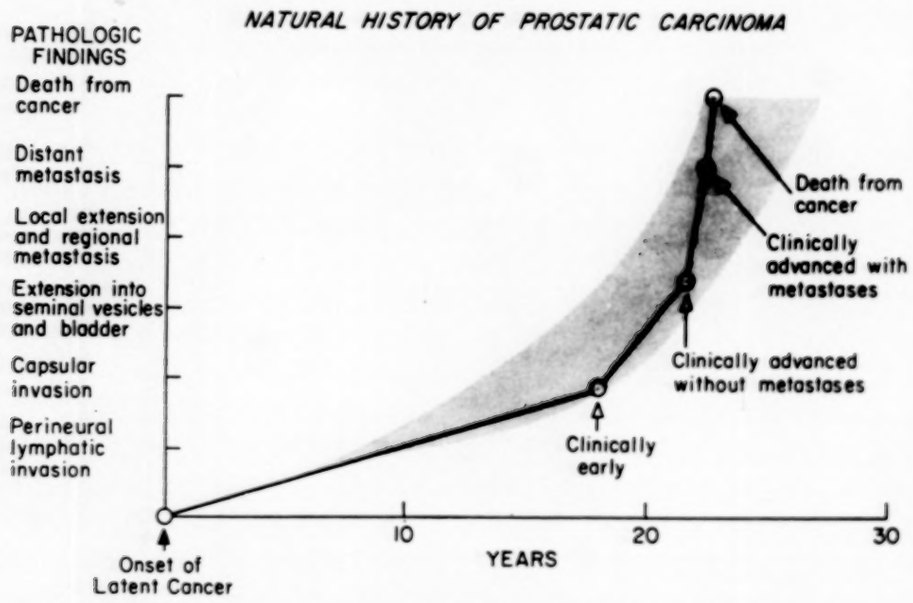


FIG. 2. Diagrammatic representation of natural history of patients with "untreated" prostatic cancer. Duration is indicated on the abscissa and extent of the disease on the ordinate. The shaded area is indicative of the potential for variation in natural history. No literal interpretation is permissible.

Hirst and Bergman[11] have presented data suggesting that the period of latency is about twenty years.

Stage II. No data have been published regarding the duration of life in patients with untreated stage II prostatic cancers, nor is there information regarding the time involved in the development of a stage III from a stage II lesion.

Stage III. The duration of survival from diagnosis to death in patients with untreated stage III lesions probably averages between two and three years. The reported three- and five-year survival rates in such patients are 22 per cent and 10 per cent, respectively.[16,17]

Stage IV. The duration of survival from diagnosis to death in patients with untreated stage IV lesions probably averages between one and two years, and the reported three- and five-year survival rates in such patients are 11 per cent and 6 per cent, respectively.[16,17] The interval between the development of a stage IV from a stage III lesion is probably about one year.

It is clearly apparent that information on the temporal aspects of the natural history of prostatic cancer is very limited and even this limited information can be justifiably criticized. Granting the probability that the approximations from present data are in considerable error, they provide a tentative basis and the only available basis for an assessment of the natural history of the disease. Figure 2 is an attempt to present this tentative estimate of the natural history of prostatic cancer in more assimilable form. The pathologic extent of the disease is represented on the ordinate and time on the abscissa. No literal interpretation of this figure is permissible!

DIAGNOSIS

The diagnosis of prostatic cancer is dependent upon pathologic examination of prostatic tissue. However, in clinical experience the following symptomatic and physical manifestations, laboratory technics and pathologic studies may be helpful in detection of such neoplasms.

1. Symptomatology. (a) Symptoms due to the primary effect of the local growth. These include frequency and nocturia, diminution in the caliber of the urinary stream, dysuria and hematuria. (b) Symptoms due to the secondary effects of the local growth. These include manifestations of upper urinary tract obstruction and/or infection, manifestations of rectal obstruction and/or irritation, and manifestations of invasion of the urethral sphincter and/or corpora of the penis. (c) Symptoms due to metastases to lymph nodes, bone, liver and/or lung. (d) Symptoms due to prostatic fibrinolysin in the circulation.[18,19]

2. Physical manifestations. (a) Digital rectal examination of the prostate is or should be a universally applied detection procedure. Jewett[20] found that a palpable nodule of induration confined to the prostate was cancer in about 50 per cent of men over forty years of age in whom there was no roentgenographic evidence of calculus. Localized prostatic indurations may result from calculus, tuberculosis, areas of non-specific inflammation, fibrosis or small capsular adenomas but one or more of these causes of induration may coexist with cancer. Not all prostatic nodules are cancer, nor do all prostatic cancers present as nodules! Hudson et al.[4] found that only 23 per cent of patients proved by open perineal biopsy to have prostatic cancer had findings suggestive of carcinoma at the time of preoperative digital rectal palpation of the prostate. (b) Other physical manifestations. Locally advanced and/or metastatic prostatic carcinoma may give rise to a wide range of physical signs which need not be detailed here. The primary tumor may be readily recognized when the local findings in the prostate are "typical," but when the primary tumor is "occult" diagnosis may be difficult unless the possibility of prostatic cancer is deliberately explored. Because of the simplicity, relative safety and usually salutary effect of endocrine therapy in the patient with advanced prostatic cancer, a special effort should always be made to eliminate or establish this diagnostic possibility in any elderly male patient with a disseminated cancer. If such effort proves inconclusive, there is rarely much risk in a therapeutic trial on estrogen.

3. Application of the Papanicolaou technic to the examination of smears of prostatic fluid obtained by massage has considerable potential in theory but has in actual practice proved disappointing.[21–23] Possible reasons for the failure of the method include: (a) the cancer cell may be present but unrecognized in the prostatic fluid; cytologic differences between the normal prostatic epithelial cell and the cancer cell may be small or ordinarily recognizable differences may be obliterated during preparation of the material; and (b) the cancer cell may not get into the prostatic fluid. The difficulties in obtaining a fully representative sample of prostatic fluid from a compound racemose gland, especially when the most dexterous massage cannot reach the anterior portion of the prostate, are obvious. Poor sampling seems to be the most important factor since the frequency of positive smears increases progressively from the stage II through the stage IV lesions.[21]

4. Serum acid phosphatase determinations. Woodard[24] found elevations in serum acid glycerophosphatase in 78 per cent of patients with prostatic cancer metastatic to soft parts but not involving bone (stage IV), 74 per cent of patients with prostatic cancer metastatic to bone (stage IV), 31 per cent of patients with locally extensive prostatic cancer without evidence of metastases (stage III), and 5 per cent of patients with cancers confined to the gland (stage II). Many urologists believe that an elevated serum acid phosphatase is, *per se*, evidence of local inoperability and/or of metastases, and would classify patients with such elevations in stage III or IV in spite of the absence of other evidences of locally extensive or metastatic disease. That this attitude has some basis in fact is indicated by the observations of Ganem[25] demonstrating that, among patients with clinically advanced prostatic cancer without demonstrable metastases to bones or lymph nodes, the prospect for five-year survival is less if the serum acid phosphatase is elevated than if it is normal. It is important to remember that transient elevations in serum acid phosphatase may result from prostatic massage and prostatic trauma.[26–28]

Abdul-Fadl and King[29] first pointed out the inhibitory effect of L-tartrate on acid phosphatase of prostatic origin. Fishman et al.[30] applied this observation clinically in the differentiation between serum acid phosphatases of prostatic and non-prostatic origins and proposed that the L-tartrate-inhibited (or prostatic) fraction of the serum acid phosphatase might be increased in carcinoma of the prostate, either localized or metastatic, when the total serum acid phosphatase was normal. Cline and coworkers,[31] using a somewhat different technic of assay, reached similar conclusions. There is no doubt that serum prostatic acid phosphatase values may be elevated in certain prostatic cancers when the total serum acid phosphatase values are still within the normal range, but the occurrence of falsely positive values and falsely negative values limits the practical value of the technic as a detection procedure.[31–33]

5. Needle aspiration biopsy of the prostate performed through the perineum or rectum is a simple procedure. Its chief application is in the pathologic confirmation of clinically obvious stage III and IV cancers. Since a large sampling

error obviously exists with this procedure, it is apparent that detection of all but the largest of clinically latent cancers (stage I) by this technic is a matter of pure chance. The incidence of positive aspirations increases with the stage of the cancer.[21] Aspiration biopsy of a suspicious nodule confirms the suspicion of cancer if a positive aspiration is obtained but does not eliminate the possibility of cancer if the aspiration is negative.

TABLE III
DETECTION OF CARCINOMA OF THE PROSTATE

Detection Technic	Percentage Accuracy in Detection			
	Stage I	Stage II	Stage III	Stage IV
Symptoms	0	0	75	100
Digital rectal examination of prostate	0	100%	100%	95+%
Papanicolaou smear of prostatic fluid	0+	17–25%	42%	90%
Serum acid phosphatase	0	0–5%	31%	74–78%
Aspiration biopsy of prostate	0+	50–71%	72%	90%
Incidental prostatic surgery	50%	16+%	100%	<100%
Open perineal biopsy	75%	100%	100%	<100%

6. Incidental prostatic surgery, usually performed for the relief of benign prostatic obstruction, undoubtedly leads to the detection of more clinically latent prostatic cancers than any other commonly employed procedure. Reference has already been made to the fact that clinically unsuspected cancer is detected in about 10 per cent of surgical specimens removed by enucleation prostatectomy. This can be considered to be approximately 50 per cent of the clinically latent cancers otherwise anticipated in this age group. On this basis, incidental prostatic surgery can be assigned an accuracy of 50 per cent as a method for detection of clinically latent cancer.

7. Open perineal biopsy of the prostate, as proposed by Hudson and coworkers,[4] has already been discussed. It comes closer to revealing clinically the established incidence of latent prostatic cancer demonstrated by autopsy studies than does any other detection procedure and has an accuracy in this regard of approximately 75 per cent.

Table III indicates the frequency with which the various methods discussed in the preceding paragraphs are helpful in the detection of the four clinical stages of prostatic cancer. Elaboration on some of the facets of detection for each of the stages follows.

Stage I: By definition, the clinically latent prostatic cancer presents no symptoms or signs attributable to its presence. Benign prostatic enlargement and/or benign prostatic indurations may be present also and may of course produce symptoms and/or signs. Latent prostatic cancers produce no consistent, detectable alteration in serum acid phosphatase. As already indicated, attempts to detect latent cancers by application of the Papanicolaou technic to the study of specimens of prostatic fluid have been disappointing, and aspiration biopsy involves such a large sampling error that only occasional successes from its use can be anticipated.[34]

For latent prostatic cancer, the practical alternatives are either to accept the disease as a clinically non-detectable condition to be accorded attention only when and if it is found incidentally by the pathologist during examination of prostatic tissue removed for reasons other than prostatic cancer, or to make a deliberate effort to detect the disease by open perineal biopsy in a defined segment of the male population.[4]

Stage II: By definition, clinically manifest early prostatic cancer presents no symptoms directly attributable to its presence, but other prostatic disease may of course coexist. Digital rectal examination, by definition, reveals a varying degree of nodularity and induration in 100 per cent of the cases. The Papanicolaou stain was positive in 17 to 25 per cent and an aspiration biopsy specimen was positive in 50 to 71 per cent of the stage II cases studied by Kaufman et al.[21] Serum acid phosphatase values have been found elevated in 5 per cent of patients whose lesions otherwise qualify as stage II growths.[24] Whether such elevations should or should not disqualify a tumor for classification as a stage II growth is debatable.

Incidental prostatic surgery does not reveal pathologic evidence of all stage II lesions. This is a reflection of the fact that stage II lesions may be confined to the peripheral portion of the gland. Kaufman et al.[21] obtained positive biopsy specimens by transurethral prostatic resection in only one of sixteen stage II lesions confirmed by open perineal biopsy. The difference apparent in Table III concerning the fre-

quency with which stage I and stage II lesions are revealed by incidental prostatic surgery is not as paradoxical as it seems. One must bear in mind that the method of classification into stages is clinical and not pathologic, and that some of the stage I cancers are actually larger in size than some of the stage II lesions. Open perineal biopsy, of course, establishes the diagnosis in 100 per cent of the stage II lesions.

Stage III: Clinically manifest advanced prostatic cancer without evidence of metastasis usually presents with local manifestations of the disease. Urinary symptoms commonly predominate but other evidences of advanced local disease may also be present. Rectal digital examination discloses the diagnosis, often supported by the results of the Papanicolaou smear, sometimes suggested by an elevated serum acid phosphatase, usually confirmed by aspiration biopsy and always established by incidental prostatic surgery or open perineal biopsy.

Stage IV: Clinically manifest advanced prostatic cancer with evidence of metastasis usually results from the progression of a stage III lesion but occasionally exhibits evidence of distant metastases when the primary lesion is not evident on rectal digital examination ("occult" prostatic cancer). Although symptoms are always present in stage IV lesions the manifestations often result more from the metastases than from the primary lesion. In stage IV growths the diagnosis is usually confirmed by the serum acid phosphatase level and by the Papanicolaou smear, and pathologic confirmation can almost invariably be obtained by aspiration biopsy, incidental prostatic surgery or open perineal biopsy, the exceptions being provided by the "occult" cancers alluded to previously.

TREATMENT

The general aim of treatment is to prolong life with comfort when possible, and at the least, to provide comfort if life cannot be prolonged. Since all forms of therapy carry some risk to life, to comfort, or commonly to both, the risk of the therapy proposed in any particular situation should be less than the risk of the cancer in that particular situation. The clinical judgment involved in making a therapeutic decision obviously demands consideration not only of the natural history of the tumor but also the "natural history" of the host. That the natural history of prostatic cancer is poorly defined has already been demonstrated; that the natural history of the host is difficult to define is evident from everyday clinical experience. Doing what one believes to be right provides the moral justification for therapeutic excursions into the valley between these two mountains of ignorance, and what one believes right may, depending upon the circumstances, vary from virtual therapeutic nihilism at one extreme to the most radical therapeutic efforts at the other.

The major therapeutic choices in the patient with a prostatic cancer are three: (1) no treatment, (2) surgical excision, and (3) endocrine therapy. Of these major therapeutic alternatives only surgical excision is potentially curative, the programs of non-treatment and of endocrine therapy being palliative only. Accordingly, the initial decision must generally determine whether therapy is to be aimed at cure or at palliation. Methods of therapy for prostatic cancer other than the three major alternatives mentioned will be considered in discussing the specific therapy of each of the four clinical stages of the disease.

No Treatment. The rationale of non-treatment is based on either or both of two considerations: (a) Host-tumor relationships such that the tumor *per se* is not believed to offer significant threat to the life and/or comfort of the host. Such a therapeutic approach is justified when the natural history of the particular tumor is thought to be relatively longer than the natural history of the particular host. (b) The tumor, for one reason or another, is not to be treated by surgical excision. In such circumstances palliative endocrine therapy may be justifiably postponed until symptoms warrant treatment.

The major advantage of a policy of non-treatment is that the patient escapes the inconveniences and risks of therapy. The major disadvantage is that the neoplasm may not behave as anticipated and that a lesion originally operable may be made inoperable by the delay incident to non-treatment.

Surgical Excision. The rationale of surgical excision is based on the belief that the only prospect of complete and permanent eradication of a prostatic cancer rests with complete surgical removal. The advantage of surgical excision resides in the possibility of "cure" which it offers. The disadvantages of surgical excision are the risks and inconveniences resulting from the surgery and the possibility that cure will not be attained.

Surgical excision of prostatic cancer has been

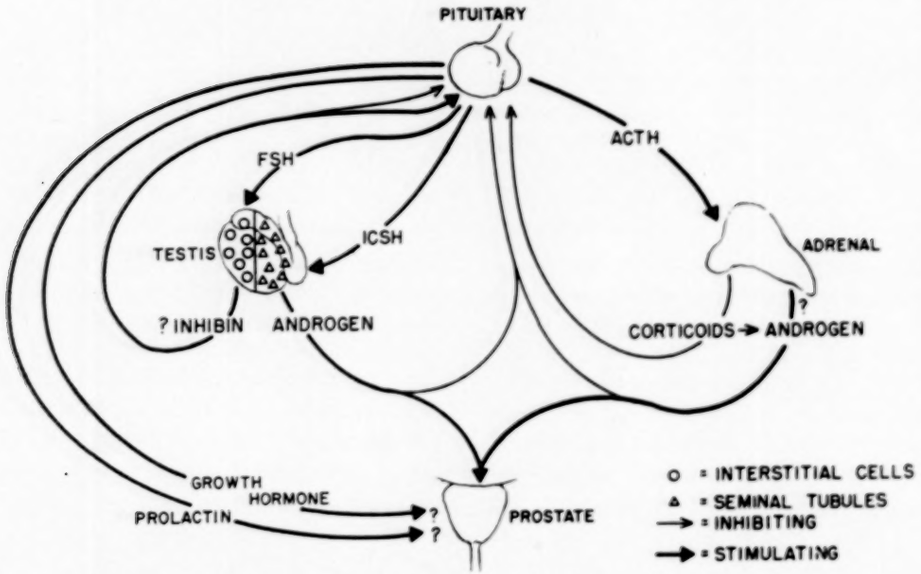


FIG. 3. Diagram illustrating established and/or conceivable endocrine influences of the pituitary gland, adrenals and testes upon the prostate.

attempted with the following variety of procedures: (a) Radical prostatectomy, removing the entire prostate and seminal vesicles with their fascial coverings and the neck of the bladder. This may be accomplished through either a perineal[35] or a retropubic approach.[36] (b) Radical prostatectomy plus dissection of pelvic lymph nodes. (c) Radical cystectomy,[6] removing bladder, prostate and seminal vesicles with adjacent fat, fascia, peritoneum and pelvic lymph nodes. (d) Pelvic exenteration[6] involving radical cystectomy plus excision of the rectum.

The risk and inconvenience increase as the operative procedure becomes more extensive. For radical prostatectomy the operative mortality is less than 5 per cent, but impotence is invariable and 10 per cent of the patients are more or less incontinent of urine. For radical cystectomy and pelvic exenteration the operative mortality ranges from 13 per cent to 21 per cent;[37] the patients will, of course, be impotent, and all suffer the hazards and inconveniences of urinary and sometimes fecal diversion.

Endocrine Therapy. The applications of endocrine therapy in prostatic cancer are logically dependent first, upon knowledge of the endocrine factors concerned in normal prostatic growth and/or function, and second, upon evidence that prostatic cancer retains a dependence upon the same endocrine factors as does the normal prostate. Concerning both of these aspects information is fragmentary. The pituitary-adrenal-gonadal relationships which are of proved or possible importance in prostatic growth and/or function are diagrammed in Figure 3 and it will be convenient to refer to this diagram in discussing the rationale of the various endocrine measures employed in the therapy of prostatic cancer. These endocrine measures include: castration, estrogen therapy, combined castration and estrogen therapy, adrenalectomy, adrenal corticoid therapy, and hypophysectomy.

In evaluating the therapeutic response to endocrine therapy the following criteria may be employed:

I. Symptomatic criteria
   (a) Changes in bone pain
   (b) Changes in urinary symptoms
II. Objective criteria:
   (a) General
      (1) Weight gain
      (2) Improved hemogram
      (3) Improved survival time
   (b) Specific
      (1) Change in prostatic lesion
      (2) Change in soft part metastases
      (3) Change in metastases to bones
      (4) Change in serum acid phosphatase
      (5) Change in serum alkaline phosphatase

Castration: White[38] in 1893 demonstrated atrophy of the muscular and glandular elements of the prostate in dogs following castration and

subsequently[39] reported favorable results in a group of patients castrated because of prostatic enlargement. It remained, however, for Huggins and his associates[40–42] to demonstrate clearly in dogs the physiologic dependence of the prostate on androgen and to apply this knowledge to the therapy of prostatic neoplasms in human beings.

The favorable action of orchiectomy may be attributed to the direct removal of the body's chief source of androgen. The advantages of orchiectomy rest with its prompt therapeutic effectiveness, its simplicity and the avoidance of side effects produced by estrogen therapy. Although every man rightly objects to the removal of his testes, a brief explanation will usually suffice to convince the most tenacious individual of the necessity for the sacrifice. Among the inconveniences of the therapy are the loss of libido, occasional complaints of loss of general physical vigor and occasional instances of annoying hot flushes. The latter usually disappear spontaneously within a few months.

Estrogen therapy: The beneficial effects of estrogen therapy[43] in the patient with prostatic cancer may be ascribed to a pharmacologic castration resulting from inhibition of pituitary gonadotrophins (FSH = follicle stimulating hormone, ICSH = interstitial cell stimulating hormone). The possibility of a supplemental favorable effect of estrogen through one or more of the following mechanisms has not been excluded, but, if present, they seem to be of secondary importance: (1) competitive inhibition of residual testicular androgen and/or of androgen of adrenal origin; (2) direct action of estrogen on the prostatic cancer cell; (3) inhibition of production or action of pituitary growth hormone; and (4) inhibition of production or action of pituitary prolactin.

The advantage of estrogen therapy rests with the fact that the testes can be left *in situ* and no operation is required. On the other hand, the therapeutic response to estrogen is somewhat slower than that to castration and the side effects of estrogen are not always inconsequential. Loss of libido and loss of physical vigor occur with estrogen as with castration but hot flushes are absent. Gastrointestinal intolerance, consisting of nausea, occasionally with vomiting, occurs in some patients receiving estrogen therapy but can usually be readily controlled by reducing dosage, shifting to a different estrogenic substance or prescribing the medication at night before retiring. In most patients gynecomastia will develop within a month of the onset of estrogen therapy but in a few patients no definite changes of the breast occur. Sometimes changes in the breast are sufficiently marked to become a source of considerable mental and physical annoyance to the patient—a fact which cannot be disregarded in one's therapeutic plans, not only because the patient may spontaneously elect to discontinue the medication but also because discomfort so induced reduces the total palliative value of the treatment.

Instances of apparent primary cancer of the breast developing after prolonged estrogen therapy in patients with prostatic cancer have, when carefully studied, been demonstrated to be metastases from the prostatic cancer.[44] In addition to gynecomastia, other feminization effects become increasingly apparent with time. The growth of facial hair thins and slows although it does not cease. Fat is deposited over the hips and pubis. The skin becomes thin and assumes a finer texture. The male pubic escutcheon may become female in type and the genitalia decrease markedly in size. In practice the psychic effect of the feminization induced by estrogen has often appeared to be more disturbing than that of orchiectomy and certainly the general physical results of estrogen therapy are more evident than those of castration.

Retention of sodium and chloride as a result of the administration of estrogen[45] is a well established clinical phenomenon. In patients of the prostatic cancer age group the incidence of cardiovascular and renal diseases is such that this action of estrogen cannot be disregarded.

Combined castration and estrogen therapy: The rationale of combined therapy is the possibility that estrogen may have one or more of the favorable supplemental actions mentioned in the previous section on estrogen therapy. Combined therapy has the disadvantages of estrogen therapy and of orchiectomy and except for a possibly beneficial effect on survival time has no recognizable advantage over castration alone.

In spite of the relatively large number of patients who have received endocrine therapy for carcinoma of the prostate there is a serious dearth of well documented studies providing information on the relative effectiveness of orchiectomy alone, estrogen alone, and the combination of orchiectomy and estrogen in the treatment of the various clinical stages of the disease. Furthermore, the available data

often give no quantitative information regarding the various symptomatic and objective criteria of improvement. As a consequence much of the discussion which follows is couched in general terms.

Although the degree of improvement following endocrine therapy by any of the three modalities discussed obviously depends in part upon the stage of the cancer at the time treatment is initiated, a favorable symptomatic and/or objective response may be anticipated in not less than 70 per cent of the cases.[46]

The changes which may accompany a favorable response may include:

Symptomatic changes: Improvement in the pain of metastases to the bones. The majority of metastases to the bones from prostatic cancer are osteoblastic and pain from such lesions will usually subside within one to five days post-orchiectomy and within five to fifteen days after the initiation of estrogen therapy. In some instances the pain relieving effect of castration will be manifest within a few hours of surgery, a fact suggesting that some rapid reduction in volume of tumor may be responsible. In the latter regard it is of interest that Rudolph and Starnes[47] found a transient increase of the "sodium space" water of the seminal vesicles and prostates of castrated rats after a single injection of testosterone propionate. When the metastases to the bone are osteolytic, pain may not disappear until the bone has recalcified, a process requiring weeks for its completion.

Urinary symptoms resulting from prostatic cancer are usually relieved, at least in part, within a few weeks of beginning treatment but when marked obstruction is evident at the start of therapy the use of a catheter or some surgical procedure may be necessary.

Objective changes: General: Irrespective of the method of endocrine treatment selected, patients who have become anemic and have lost weight show a gradual improvement in both features.

Specific: Again irrespective of the method of endocrine therapy, patients will usually demonstrate a decrease in size and induration of the primary prostatic tumor and a decrease in size or even disappearance of soft part metastases. The changes in the bone lesions as demonstrated by x-ray are sometimes confusing. In spite of symptomatic and general clinical improvement, serial x-rays of the bone will often reveal extension of the osteoblastic process, at least initially. Although this is roentgenographically interpreted as extension of disease it seems probable that it often represents a "salting out" of pre-existing "soft" metastatic deposits in bone or bone marrow. This explanation is often supported by the general condition and progress of the patient and by the fact that on rare occasions the osteoblastic reaction will in time disappear leaving a relatively normal appearing bone on roentgenographic examination.

An elevated serum acid phosphatase tends to fall within a week of castration and within two to three weeks after initiation of estrogen.[48] The serum alkaline phosphatase is usually elevated in patients with metastases to the bone from prostatic cancer and often shows a further rise or a sustained plateau of activity following endocrine therapy.

Gross reductions in the size of the tumor accompanying such favorable responses are reflected in microscopic evidence of the destruction of the tumor cell in the prostate and in soft part metastases.[43]

Recurrence of symptoms is usually the first evidence of relapse in the patient with prostatic cancer who has obtained a remission from endocrine therapy. Bone pain is commonly the first symptom of such reactivation but urinary symptoms may predominate. Occasionally weakness and weight loss will dominate the clinical picture of recurrence. Reactivation of the primary prostatic lesion may or may not occur. The acid phosphatase may remain normal, even if it was initially elevated, suggesting that some fundamental change has taken place in the tumor; this is suggested also by the fact that it is sometimes the development of new metastases rather than the recrudescence of old ones which dominates the clinical picture in relapse. If either orchiectomy or estrogen has been untried in the relapsed patient, such should be promptly initiated. Although secondary remissions so induced are symptomatic only and transient, there is little to be lost by the effort since the average duration of survival from the time of relapse is less than ten months.[46] Seventeen to 36 per cent of patients will obtain a brief symptomatic secondary remission from such effort.[46]

With respect to the dosage and preparation of estrogen used there is little objective information on which to base a choice of drug or dosage. Baker[50] found that as little as 0.25 mg. of diethylstilbestrol intramuscularly daily would

bring about a remission in a patient with prostatic carcinoma. Birke et al.[51] found that oral administration of 30 mg. of diethylstilbestrol daily to patients with prostatic cancer produced a maximum reduction in urinary androsterone, etiocholanolone and total 17-ketosteroid excretion, which could not be further reduced by increasing the dosage of estrogen. Although these observations suggest that 30 mg. of diethylstilbestrol daily is a logical maximal dose, there are no clinical observations to support this suggestion. In the collective review of Nesbit and Baum[46] the patients were treated with the equivalent of 1 to 5 mg. of diethylstilbestrol daily. However, Hudson et al.[4] have used 500 mg. of diethylstilbestrol daily. The situation can be accurately summarized by saying that there is no unanimity of opinion on estrogen dosage and that no clear cut clinical evidence has yet been assembled to indicate an advantage for any particular dosage level, provided only that the minimal effective dose has been exceeded.

With regard to the preparation of estrogen employed, no one substance has demonstrated any superiority over any other as far as control of the prostatic cancer is concerned. The drugs most commonly used in this country are diethylstilbestrol, ethinyl estradiol* and tri-*p*-anisylchloroethylene.† When a patient has relapsed from one estrogen preparation in one dosage, objective evidence of a further remission by changing the estrogen preparation or the dosage, or both, has not occurred.

When the diagnosis of prostatic cancer has been made and when the therapeutic decision calls for palliation only, there is the question, when should the endocrine treatment be initiated. Some favor immediate treatment whether or not the disease is symptomatic; others favor immediate treatment *only* when the disease is symptomatic and, in asymptomatic situations, advise delaying endocrine therapy until symptoms appear. There is no convincing evidence, either in terms of patient comfort or survival, categorically to support or refute either of these therapeutic philosophies.

Although remissions from the aforementioned modes of endocrine therapy may last for ten or more years, these are the exceptions. Good data on the extension of survival contributed by endocrine therapy are surprisingly scarce considering the large numbers of patients treated but the average extension of life so afforded is probably between one and two years.[46,52]

The reasons for relapse and the reasons for initial failure to respond to endocrine therapy may be the same, but in any event are unknown.

Adrenalectomy: The rationale of adrenalectomy in the treatment of cancer of the prostate is dependent upon two postulates for which there is specific although incomplete evidence:[53] (1) that prostatic cancer is an androgen-dependent tumor and that this androgen dependence is at least in part retained in the relapse following castration and/or estrogen therapy, and (2) that the relapse following castration and/or estrogen therapy is the result of androgen derived directly or indirectly from the adrenal gland.

Adrenalectomy, although a major operative procedure, can be accomplished with minimal mortality and morbidity. The therapeutic results from the procedure have, however, been generally disappointing as evidenced by the facts that:[53–55] (1) life expectancy is not extended by the procedure; (2) subjective remission in pain and/or in urinary symptoms has occurred in approximately half of the patients but has been unpredictable in occurrence and usually short in duration; and (3) objective evidence of remission has been obtained in about 10 per cent of the patients but has been unpredictable in occurrence and usually short in duration.

There are several possible reasons for the poor results of adrenalectomy: (1) The cortisone or hydrocortisone replacement therapy required after adrenalectomy prevents the ideal of an "androgen-free" environment for the prostatic cancer since some of the metabolites of these substances are androgenic. The studies of Harrison et al.[56,57] and Munson et al.[58] suggest that this argument is more of academic than of clinical importance since the amount of androgenic activity is so small. (2) The possibility that therapeutic failures following adrenalectomy result from the fact that the prostatic cancer has already become androgen-independent at the time adrenalectomy is performed. Morales et al.[54] have largely eliminated this possibility by demonstrating that adrenalectomy carried out as the initial endocrine therapy of prostatic cancer was no more effective than adrenalectomy performed after relapse from a castration-induced remission. (3) Graham's[59] observation

* Estinyl® (Schering).

† TACE® (Wm. S. Merrell Research Laboratories).

that accessory adrenocortical tissue was present in the region of the celiac plexus in thirty-two of one hundred consecutive autopsies suggests that bilateral adrenalectomy may fall short of total adrenalectomy in about one-third of the subjects.

In spite of the fact that adrenalectomy has been disappointing as a means of therapy, one cannot escape the interesting fact that many patients so treated had subjective remissions and a few had objective regressions of the cancer. These observations, although perhaps not justifying a general application of this therapeutic modality, at least justify further clinical exploration with the hope that a method may be found for detecting preoperatively which patient may be expected to obtain sufficient benefit from the procedure to warrant its performance.

Adrenal corticoid therapy: This is based on the belief that androgen resulting directly or indirectly from adrenal secretions may be reduced as a result of a decrease of endogenous adrenal steroid production brought about through depression of ACTH by the exogenous steroid. Support for this possibility is provided by the demonstration of a marked increase in urinary androgen excretion following the administration of ACTH to both intact and castrated men with prostatic cancer[58] and by the observation of a marked decrease in urinary androsterone and etiocholanolone excretion following the administration of cortisone to both intact and castrated men with prostatic cancer.[51] The rationale of this method of therapy in the treatment of prostatic cancer is dependent upon the same two postulates enumerated for the rationale of adrenalectomy.

Adrenocorticoid therapy has the advantages of simplicity and convenience, and the disadvantages of the risks incumbent in the administration of these substances to the eucorticoid individual, such as, gastrointestinal ulceration, salt retention, potassium depletion and the like.

Valk and Owens[60] reported 40 per cent improvement with massive cortisone and estrogen therapy in a series of twelve patients with advanced prostatic cancer who were in relapse following castration and estrogen. Three of five improved patients had survived a year or more and two of the five had had reductions in serum acid phosphatase. Miller and Hinman[61] treated ten similar patients with 50 mg. of cortisone daily by mouth and observed subjective improvement in eight and objective improvement in six, but the duration of the favorable responses was less than three months. Harrison, Thorn and Jenkins[55] treated nine similar patients with cortisone in small doses. Although eight of the nine had some subjective improvement, none showed objective evidence of tumor regression. Experience with cortisone is accumulating and the impression is gained that, as in the case of adrenalectomy, subjective improvement is common but of short duration, and objective evidence of tumor regression is rare.

Hypophysectomy: The logic of hypophysectomy in the prostatic cancer patient who is in relapse following a remission induced by castration and/or estrogen is dependent upon a number of suppositions for which the evidence is at best quite fragmentary: (1) that adrenalectomy failures may be the result of incomplete adrenalectomy and that this problem could be circumvented by the physiologic adrenalectomy which would result from the loss of ACTH stimulation via hypophysectomy; (2) that growth hormone may be a factor in human prostatic growth and/or function; and (3) that prolactin may be a factor in human prostatic growth and/or function.

The potential role of incomplete adrenalectomy as a factor in the therapeutic failures following adrenalectomy has already been mentioned.

Evidence that growth hormone is specifically involved in the growth and/or function of the normal prostate of man or experimental animals is lacking but its apparent role as a general anabolic factor in the genesis, growth or maintenance of a variety of experimental tumors has been well demonstrated.

Evidence that prolactin may be a factor in prostatic growth is provided by Sonenberg's[62] observation of the localization of I-131 labelled prolactin in the rat prostate and by the observations of Grayhack et al.[63] concerning the ability of prolactin to augment the effect of testosterone on the prostate of the hypophysectomized castrate rat.

Hypophysectomy can best be regarded as a clinical experiment in the treatment of patients with prostatic cancer. At Memorial Center eight patients with proved, advanced prostatic carcinoma in relapse after castration and/or estrogen therapy have had hypophysectomy. One patient died less than one month postoperatively and could not be evaluated. Seven patients were evaluated. Hypophysectomy was

functionally incomplete in one of the seven and this patient failed to show subjective or objective remission. The remaining six patients had functionally complete hypophysectomies. Four of these survived one to eight months without subjective or objective improvement. The remaining two patients have had remissions. One experienced a remission in pain, an improvement in paraplegia and a fall in serum acid phosphatase which lasted eleven months before the onset of relapse; the other has had striking relief of pain, a rise in hemoglobin and disappearance of edema of the legs for four months since operation, but his serum acid phosphatase has risen slightly. Thus two patients among the eight achieved subjective remissions from hypophysectomy and one of these two had an apparent objective regression as evidenced by a fall in serum acid phosphatase. Much more experience will be necessary to evaluate fully the effects of hypophysectomy in prostatic cancer.

CHOICE OF THERAPY AND RESULTS

Having outlined the rationale, advantages and disadvantages of the major therapeutic alternatives, their application to the different clinical stages of prostatic cancer can now be considered. (Table IV.)

Stage I. Difficulties in the clinical detection of latent prostatic cancer somewhat simplify the problem of treatment since undiagnosed cancers create no overt problem in therapy.

Non-treatment: The natural history of latent prostatic cancer is incompletely defined. Some probably experience a 10 to 20 year period of latency, some manifest themselves ultimately as "occult" carcinoma, destroying the patient with metastatic disease before the primary tumor ever becomes clinically manifest. An estimate of the prognosis of patients with untreated stage I lesions is afforded by: (a) The data of Higbee[64] who found eight instances of stage I cancer during incidental prostatic surgery. Three of these patients died of causes other than carcinoma but the others were alive without recurrence or metastasis five years later. (b) The data of Edwards[65] who found twenty-three instances of stage I cancer during incidental prostatic surgery. Two subsequently died of cancer, five died of unrelated causes and the remaining sixteen were alive without recurrence or metastasis five years later. (c) The data of the Hinmans[66] who found that the average survival of nine patients with stage I lesions treated by transurethral resection alone was 36.8 months. (d) The data of Greene and Simon[67] who found a 73 per cent five-year survival rate in thirty-seven patients whose stage I cancers were treated by transurethral resection alone. Since the average five-year life expectancy of patients of this age group[67] was about 75 per cent, it is apparent that 75 per cent would be the maximal attainable five-year survival rate even if no patient died of cancer.

TABLE IV
SURVIVAL WITH DIFFERENT FORMS OF THERAPY IN CARCINOMA OF THE PROSTATE

Clinical Stage of Neoplasm	Method of Management		
	No Treatment	Surgical Excision	Endocrine Therapy
Stage I	? 10–20 yr. 70% 5 yr.	75% 5 yr.	67%
Stage II	?	61% 5 yr. 37% 10 yr.	53% 5 yr. 22% 5 yr.
Stage III	10% 5 yr.	0+	29–43% 5 yr.
Stage IV	6% 5 yr.	0	10–21% 5 yr.

These limited data, the Hinmans' study excepted, suggest that the five-year survival rate among patients with occult prostatic cancers is about 70 per cent, a figure very close to the expected "natural" survival rate for individuals of this age group. This high survival rate may be attributable in part to the slow growth of the tumor and in part to the possibility that the tumor was completely removed by the procedure which lead to its detection.[66] The poor correlation of the Hinmans' data with the other studies remains unexplained. Certainly, far more data must be accumulated before statistical significance can be accredited to any of the figures cited.

Surgical excision: Hudson et al.[4] have been and are continuing to do open perineal biopsies on patients in whom some type of definitive prostatic surgery is being contemplated. When latent carcinoma is so identified, radical perineal prostatectomy is performed, the testes are removed and the patient is started on a regimen of 500 mg. of diethylstilbestrol daily. Five-year results are not yet available.

The Hinmans[66] reported an average survival of 67.8 months in five patients submitted to radical perineal prostatectomy after latent cancer had been detected by transurethral resection. This was compared with an average survival of 36.8 months in nine similar patients who had had transurethral resection only.

Endocrine therapy: Greene and Simon[67] reported a five-year survival rate of 67 per cent in thirty-nine patients with latent prostatic cancer discovered by transurethral resection who were treated with diethylstilbestrol.

For stage I cancers the reported five-year survivals following the major methods of management are excellent and seem to approximate natural expectancy for men 68 or 69 years of age, (75 per cent 5-year survival). In the face of present information, an aggressive attitude towards either the diagnosis or treatment of latent prostatic cancer in patients in whom the five-year natural expectancy does not exceed 75 per cent is difficult to justify except as a clinical experiment. For the patient whose life expectancy apparently exceeds ten years, detection of a latent prostatic cancer may justify consideration of surgical excision, but any tendency towards therapeutic aggressiveness should be curbed by recollection of our ignorance not only of the natural history of the disease but of the results of the alternative methods of therapy.

At the present time "non-treatment" is what most individuals with stage I cancer receive, if for no other reason than lack of detection. When one considers the tremendous number of latent prostatic cancers, the death rate from prostatic cancer in this country becomes relatively less impressive. This is another way of saying that "non-treatment" has been a relatively effective method of management of latent cancer. Conservatively, there are more than 3,000,000 men in this country with such stage I cancers. Granting that diagnosis and excision of all such latent lesions would completely prevent the occurrence of "occult" cancers, the relative infrequency of the latter clinical setting would not justify the undertaking. Furthermore, the major source of present prostatic cancer mortality is still the clinically obvious prostatic cancer. The implication is that somewhere between the latent cancer that is not clinically recognized and the stage III lesion which is recognized too late there must reside a population of stage II lesions which are waiting to be recognized or at least suspected from digital rectal examination of the prostate. Efforts should be redoubled, not to detect the stage I lesion, which is so often without clinical import, but to detect the stage II lesion, the logical forerunner of a lesion of ominous prognosis.

Stage II. Non-treatment: There is no information concerning the temporal natural history of untreated lesions of this stage. Patients with stage II lesions are asymptomatic with reference to the cancer; accordingly the possibility of a program of non-treatment in this stage cannot be categorically dismissed.

Surgical excision: Radical perineal prostatectomy is the only surgical procedure for which significant survival data are currently available. Jewett[5] reported a 61 per cent five-year and a 37 per cent ten-year survival rate for patients with Stage II lesions, as compared with natural life expectancies for the age group involved of 76 per cent and 53 per cent, respectively.

Concerning the results of retropubic prostatectomy, radical prostatectomy with dissection of the lymph node, radical cystectomy and pelvic exenteration in the treatment of stage II lesions, no information of statistical value is available.

Endocrine therapy: Data regarding the use of endocrine therapy in the management of stage II lesions are limited to those of Barnes[68] who reported a 53 per cent five-year and 22 per cent ten-year survival rate in thirty-one patients, all but six of whom had estrogen therapy and/or orchiectomy. Of the fifteen deaths occurring within the first five years, five were due to causes other than cancer. In six, or 38 per cent, of the five-year survivors evidence of prostatic carcinoma subsequently developed.

For stage II cancers radical prostatectomy should probably be advised if the patient's life expectancy exceeds five years. If life expectancy does not exceed 5 years, either non-treatment or endocrine therapy is advised, bearing in mind the inconveniences of endocrine therapy and the fact that no advantage has been demonstrated for initiation of endocrine therapy as soon as the diagnosis is made. Endocrine therapy is palliative therapy and unless evidence can be brought forth in favor of its prophylactic use, it can logically be reserved until the manifestations of the disease demand its initiation.

Stage III. Non-treatment: From the point of view of temporal natural history the data of Nesbit and Baum[46] indicate a five-year survival

rate of 10 per cent for patients with untreated stage III lesions. Most stage III cancers cause local manifestations sufficient to demand treatment so that a policy of nontreatment is rarely followed.

Surgical excision: Experience with radical cystectomy and pelvic exenteration in attempts at surgical excision of stage III cancers[6] has indicated the general futility of this approach. Although metastases were not preoperatively recognized in such cases, laparotomy promptly revealed metastases to the lymph nodes almost invariably. Excisions were initially attempted even in the presence of obvious regional metastases to the lymph nodes but the high mortality, high morbidity and, above all, the high recurrence rate led to general abandonment of the procedure. In the younger patient with an "early" stage III lesion, such radical surgery may still find a place but it certainly has not yet been defined.

Endocrine therapy: Nesbit and Baum[46] found the five-year survival rate in patients with stage III lesions to be 29 per cent with estrogen therapy, 31 per cent with orchiectomy and 43 per cent with the combination of estrogen and orchiectomy.

For selected problems in patients with stage III lesions the following additional modalities of therapy are sometimes helpful: (1) transurethral resection for relief of bladder neck obstruction; (2) urinary diversion to an ileal bladder;[69] and (3) implantation of radioactive material into the tumor with or without concomitant urinary diversion. Kerr et al.[70,71] have described the technic and the results of radioactive gold injection into stage III prostatic cancers. Although the radioactive material is capable of destroying the cancer when it makes sufficiently close contact, problems of obtaining adequate and uniform distribution of the radioactive solutions have confined the technic to situations where palliation rather than cure is being sought. This is not a technic for treatment of stage II lesion unless radical excision, for one reason or another, is not to be done.

For stage III lesions the problem is generally one of palliation only, except perhaps for the relatively young man with an early stage III lesion for whom there may be hope for cure from radical cystectomy. Endocrine therapy is commonly utilized as a first method of management, employing castration first and resorting to estrogen (ethinyl estradiol 1 mg. daily) when and if castration relapse occurs. Operations for relief of bladder neck obstruction are postponed, if at all possible, in order to give the endocrine therapy a chance to relieve obstruction, but transurethral resection is done if operation is unavoidable. When and if there is ureteral obstruction and/or severe bladder dysfunction from the tumor, urinary diversion, preferably to an ileal bladder, may be considered, especially if the general condition and prognosis of the patient seem to warrant the risks. At the time of urinary diversion radon seeds or other radioactive material may be conveniently implanted into the tumor. Cortisone may be tried when all else fails but its greatest virtue is in the patient with bone pain rather than in the patient with massive local disease.

Stage IV. Non-treatment: This is rarely if ever called for in the patient with stage IV cancer. The data of Nesbit and Baum[46] indicate a 6 per cent five-year survival in patients with untreated stage IV lesions.

Surgical excision: This is obviously out of the question in the patient with a stage IV lesion.

Endocrine therapy: This offers the only hope of significantly increased survival to these patients. Nesbit and Baum[46] reported a 10 per cent five-year survival in patients treated with estrogen alone, a 21 per cent survival from orchiectomy alone and a 20 per cent survival from the combination of estrogen and castration.

For patients with stage IV lesions x-ray therapy and neurosurgical procedures for the relief of pain and for decompression of the spinal cord are occasionally desirable. For first therapy castration is carried out. When relapse occurs a trial on estrogen, usually ethinyl estradiol 1 mg. daily, is begun. When estrogen failure is apparent the choice rests between radiation therapy and cortisone. If pain is localized and severe enough to warrant concern, radiation therapy is given. A tumor dose of 2,000 r delivered in ten to fourteen days with a 250 KV unit will usually provide between six weeks and three months of relief. A second and even a third course may, if necessary, be given to the same area with success. If the prospects of repeated courses of radiation seem good, practical advantages may result from use of 400 KV or 1,000 KV units. If pain is or becomes generalized, cortisone may be tried, commonly starting with 50 mg. every six hours for five days, followed by 50 mg. every twelve hours for ten days, and adjusting dosage

to lower levels thereafter if possible. Adrenalectomy and/or hypophysectomy are still to be regarded as experimental methods of therapy.

SUMMARY

A survey of the prostatic cancer problem is presented, including the pathology, clinical classification, incidence, natural history, diagnosis, methods of treatment, choice of treatment and results. The endocrine aspects of therapy have been particularly stressed since this is the most practical and promising therapeutic approach in the majority of patients.

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Abnormalities in Calcium Metabolism in Malignancy; Effects of Hormone Therapy*

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BONE represents one of the most frequent sites of neoplastic metastases, surpassed in this respect only by lungs and liver.[1] In 1891 von Recklinghausen presented a classic account of metastatic cancer of the bone.[2] Most of his conclusions have withstood the test of time. For example, he indicated that (1) metastatic growths of bone appeared first within the bone marrow; (2) they are blood-borne; (3) subperiosteal extensions appear chiefly where main foramina traverse the cortical bone; and (4) the order of frequency in different parts of the skeleton is as follows: vertebrae, proximal ends of the femur, pelvis, ribs, sternum, proximal ends of the humerus, skull, and other bones less frequently.

Although all carcinomas may metastasize to bone, those originating in the breast, lung, prostate, kidney and thyroid do so most frequently.[1] In carcinoma of the breast, the incidence of skeletal metastasis in disseminated disease varies from 50 to 75 per cent.[1,3] In a recent study of consecutive cancer patients 10 per cent of all bone marrow aspirations were positive for cancer cells and in 37 per cent of these there was no radiologic evidence of tumor.[4] The presence or absence of tumor cells as indicated by this technic may prove ultimately to be of prognostic value.[5] The prevalence of tumor cells within the marrow cavity must be due in large part to its rich vascular supply, with trapping of blood-borne tumor cells. In addition, the pelvis and lumbar spine have extensive venous anastomoses from the vena cava, as demonstrated by Batson,[6] and this must play a role in the frequency of metastatic disease in that area, especially with primary tumors of the pelvic organs. Finally, the biochemical nature of the soil which supports active marrow proliferation normally, constitutes a fertile area for the proliferation of tumor cells. As tumor cells encroach upon the red marrow, new areas of marrow production within the yellow or fatty marrow may develop and thus the mid-portions of the shafts of long bone ultimately become areas of increased vascular supply. In general, the microscopic appearance of the tumor cells within bone corresponds closely with that of the primary tumor. With destruction of bone, replacement by connective tissue stroma and tumor cells occurs and large numbers of multinucleated cells resembling osteoclasts can be seen at the site of bone destruction.[1] The reaction of the host to this bone resorption is usually that of bone formation or repair, so that in most cases a mixture of osteolytic and osteoblastic reaction is seen. If bone destruction exceeds bone production a net loss of calcium occurs and this is reflected by an increased excretion of calcium in the urine and feces. In those tumors evoking an osteoblastic reaction, when bone production exceeds bone destruction, calcium excretion in the urine is usually lower than normal. Metabolic data in the literature show that parallel increases or decreases of urinary phosphorus accompany the calcium change, most of which can be accounted for by bone destruction or production.[7,8]

Osteolytic versus Osteoblastic Metastases. As stated previously, most tumors show a combination of osteolytic and osteoblastic elements, but all variations exist. Carcinoma of the prostate ordinarily evokes a predominantly osteoblastic lesion whereas carcinoma of the thyroid characteristically produces an osteolytic type of reaction. Exact reasons for these reactions are not known but they are undoubtedly related in part to the biochemical nature of the tumor cells. In general, slowly growing tumors evoke a desmoplastic reaction in soft tissue and an osteoblastic reaction in bone. These two reactions are

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characteristic of the body's reaction to injury, which in the case of fracture is callus and in soft tissue, scar formation.

A recent pathologic analysis of metastatic cancer in bones indicates that the differences in bone response to various types of neoplasms are quantitative and not qualitative. The authors believe the type of reaction produced is due mainly to rate of tumor growth and not to any abnormal substance produced by the cancer cells.[9]

That rate of growth governs the entire repair reaction seems unlikely since very rapidly growing prostatic carcinomas produce an osteoblastic reaction and slowly growing carcinomas of the thyroid an osteolytic reaction. It is probable that in these situations biochemical characteristics of the tumor cells play an important part in determining the type of host reaction to their presence. One of many possible governing biochemical factors could be the high level of acid phosphatase which is found in prostatic carcinoma cells.[10] An acid phosphatase has also been demonstrated in carcinoma cells in the breast which produce a combination of osteolytic and osteoblastic metastasis and, in an occasional case, complete osteoblastic reaction.[11,12] Carcinoma cells of the thyroid and kidney do not contain such concentrations of this enzyme and, in addition, are notoriously poor in stroma thus failing to provide a matrix for calcium deposition to occur.

Eventually the host's defense reaction to the invading tumor cells is overcome and replacement of bony tissue by neoplastic cells results in a release of calcium and phosphorus into the blood stream which is then excreted predominantly by the kidney.[7,8,13] If the released calcium exceeds the capacity of the kidney to excrete such large quantities, hypercalcemia and its attendant symptomatology ensue. In most cases the resultant hypercalcemia is associated with a normal or elevated serum phosphorus, rarely with a low serum phosphorus, particularly when cachexia is present. When a low serum phosphorus accompanies the hypercalcemia the blood serum values are identical with those of hyperparathyroidism and there is difficulty in exact diagnosis.[14,15] A possible explanation is the production of a parathormone-like substance by the cancer cells.[15]

Renal Excretion of Calcium. Endogenous calcium excretion in man, expressed as a ratio of urine excretion to fecal excretion, is approximately two to one.[16] A similar excretion ratio exists in the monkey but in the dog the ratio is reversed to one to ten and in the rat to one to twenty-two.[17] These excretion ratios must be taken into account when metabolic experiments in the dog and rat are translated to man. With persistent hypercalcemia and hypercalciuria in cancer of the breast, metabolic experiments reveal no defect in absorption. When calcium intake is increased from 150 mg. to 1.0 gm., about 20 per cent of calcium in the intake is absorbed and retained, producing a less negative balance and very little or no increase in urinary calcium excretion.[7,18] In such patients the normal excretory ratios are usually present, the kidney playing the major role. Pearson states that when the urinary excretion of calcium exceeds 500 mg. per twenty-four hour period, hypercalcemia occurs.[19] This is generally true but in occasional patients a urinary calcium excretion as high as 900 mg. per twenty-four hours has been found to be associated with normal serum calcium.[18] In most of these latter cases an osteoblastic reaction is present within the bone so that bone production in the host may play a part in keeping the serum calcium at a normal level. In addition, changes in renal reabsorptive mechanisms may also be important in regulating serum calcium. The exact mechanism of calcium excretion by the kidney is not known but indirect evidence seems to indicate that the calcium not bound to protein is filtered and partially reabsorbed by the renal tubule.[13] Such indirect evidence indicating that calcium is probably reabsorbed can be seen in Figure 1, which demonstrates the effect of mercuhydrin on calcium excretion. This patient was on a constant calcium intake and was receiving oral meticorten, 20 mg. daily, for cancer of the breast metastatic to lungs and bone. With each injection of 2.0 cc. of mercuhydrin the concentration of calcium, in mg. per cent, rose, accompanied by a moderate to minimal diuresis with resultant increase in total calcium output. A similar change has occurred during administration of mercuhydrin to four additional patients, two of whom had no disease of the bone but all of whom were receiving cortisone therapy for varying reasons. Similar although less marked changes in normal subjects not on cortisone therapy have been reported elsewhere.[21]

During the acute phase of hypercalcemia, symptoms of dry mouth, polyuria, polydipsia and vomiting are usually present. We have

studied two patients during this phase and have demonstrated a decreased glomerular filtration rate and a decreased renal blood flow with a normal filtration fraction. Both patients were unable to concentrate well but responded normally to antidiuretic hormone.[18] When calcium

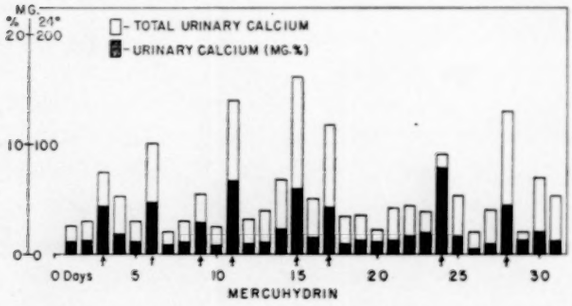


FIG. 1. The effect of mercuhydrin in a sixty-three year old woman with cancer of the breast metastatic to lungs and bones. The patient was on a constant, low-calcium (150 mg.) diet and received 20.0 mg. of meticorten orally. On eight different occasions, designated by the arrows, 2.0 cc. of mercuhydrin were given intramuscularly and each time the concentration of calcium rose with an increase in the total twenty-four hour urine output.

lactate infusions are given to normal subjects in amounts sufficient to cause hypercalcemia, increased urinary excretion of sodium and chloride accompany increased calcium excretion.[22]

With sustained hypercalcemia, deposition of calcium occurs within the renal tubules and in the renal pelvis, with eventual nephrocalcinosis and at times stone formation, leading to mechanical impairment of kidney function with a rising non-protein nitrogen. In such a situation hypercalcemia is further aggravated and therapy must be directed towards the cause to interrupt a vicious cycle.

Hypercalcemia. An elevated blood calcium can occur in many diverse pathologic states such as hyperparathyroidism, vitamin D intoxication, milk-alkali syndrome, Boeck's sarcoid and a wide variety of neoplastic diseases metastatic to bone.[15,23] It is not the purpose of this paper to discuss the distinguishing features of each of these conditions. Suffice it to say that the conventional clinical history, physical examination and laboratory analysis are usually adequate to differentiate them.

Hypercalcemia occurring in the presence of neoplastic bone involvement has been discussed at length by numerous authors.[14,24–27] It occurs spontaneously in about 10 per cent of patients with disseminated cancer of the breast and in about 20 per cent of patients with cancer of the breast treated with hormones.[28] It occurs occasionally with hypernephroma, bronchogenic carcinoma, multiple myeloma and other miscellaneous tumors metastatic to bone, but is very rare in carcinoma of the thyroid or in prostatic carcinoma. In prostatic carcinoma the excess calcium released by bone breakdown may be compensated for by the very active osteoblastic proliferation of the host. On the other hand, in carcinoma of the thyroid with little osteoblastic proliferation the reason for its absence may be related to the very slow growth rate of this type cancer. As stated previously, hypercalcemia is usually associated with a normal or elevated serum phosphorus. In the absence of disease of the liver or biliary tract, hypercalcemia is also accompanied by a normal or falling serum alkaline phosphatase, and remission from hypercalcemia by a rising alkaline phosphatase, indicating bone repair.[28,29]

In our experience we have seen no case of hypercalcemia associated with cancer that has not shown evidence of metastases to the bone either by x-ray or autopsy. Very recently two cases of bronchogenic carcinoma with hypercalcemia, hypercalciuria and hypophosphatemia, without evidence of bone disease, have been reported.[30] In one patient hypercalcemia subsided four days after removal of the primary lung tumor but recurred with metastases to the chest wall and then remitted again prior to death. Routine autopsy showed no skeletal metastases but areas of bone remote from the primary tumor showed active bone resorption without tumor cells. A second patient showed no evidence of metastases to the bone by biopsy or x-ray, and with removal of the primary tumor hypercalcemia subsided. In addition, a small series of cases of hypercalcemia with negative autopsy evidence of metastases to the bone has been seen recently at the Presbyterian and Francis Delafield Hospitals in New York. Most of these cases were of renal or ovarian origin, or located in the retroperitoneal space.[31] It is very difficult to explain such findings merely on the basis of tumor growth and osteolytic destruction of bone by tumor cells. They suggest, as Connor points out, that the tumor cells may be elaborating some substance which is capable of causing resolution of bone. The fact remains, however, that in most of these instances, the tumors described have a high

frequency of metastasis to the bone and single small areas of metastatic lesions might be missed at routine autopsy. In addition, patchy necrosis is common in osteoclastic tumors and at times this may be so extensive that tumor tissue is replaced by a structureless debris of an area several centimeters in diameter, so that the edge of the neoplasm may be devoid of living cells over a wide front.[1] Thus a small biopsy site might not include the neoplastic cells. A decrease in hypercalcemia following removal of the primary tumor is very good evidence that resorptive bone agents were being produced by the neoplastic cells. Such cases must be scrutinized carefully since, if tumor cells do release resorptive agents, our explanation of hypercalcemia and hypercalciuria in the presence of bone neoplasm will need revision.

Since sudden death may occur in hypercalcemia, successful therapy may be a life-saving maneuver. Numerous methods to lower the serum calcium with complexing and chelating agents have been tried. The administration of sodium citrate, a complexing agent, has frequently been advocated.[14] Very little lowering of the serum calcium occurs with sodium citrate since the citrate is rapidly metabolized. Attempts to lower the serum calcium by means of chelating agents such as sodium ethylenediamine tetra acetate (sodium EDTA) have not been successful.[32–34] Although a proportion of the serum calcium is bound and chelated by sodium EDTA and excreted in the urine, there is no change in the total serum calcium, which may even increase. Associated with the increase in serum calcium there is an increase in urinary calcium.[34] Finally, sodium EDTA, when given in amounts to bind the excess ionized calcium, will produce renal tubular damage with anuria and azotemia, to cause further renal impairment.[34,35]

The use of oral agents, such as sodium phytate or oral sodium EDTA, to decrease intestinal absorption of calcium may be of temporary benefit.[18,36] From a practical standpoint, however, many patients with marked hypercalcemia are nauseated and vomiting, so that the use of oral agents is not feasible. The best available means to treat hypercalcemia in carcinoma of the breast at the present time is to administer large amounts of intravenous fluid to promote the renal excretion of calcium and, by lowering of the urinary calcium concentration, prevent nephrocalcinosis. When hypercalcemia follows administration of hormones, discontinuance of the offending hormone is indicated as well as administration of large amounts of fluid. In spontaneous hypercalcemia shifts in the hormonal environment by means of castration, adrenalectomy, hypophysectomy or administration of hormones may change the tumor-host relationship to favor the host, with subsequent decrease of the elevated blood calcium.

The Effect of Hormones on Calcium Metabolism in Cancer. In the final analysis very little is known concerning the exact nature of the action of hormones on calcium metabolism in man. Most of the information is derived from indirect parameters and thus the changes that occur with administration or withdrawal of hormones must be analyzed with full awareness of the multiple known and unknown factors involved.

Aub, in 1933, reported on four patients with cancer of the breast metastatic to bone who showed slight increases in urinary calcium which he interpreted to be due to the destructive effects of the tumor on bone. Parathyroid extract administered to these patients produced the same effect as in control subjects.[37] More recently, Pearson has shown by very careful metabolic studies that fluctuations in serum and urinary calcium in patients with metastatic cancer of the breast can be correlated with hormonal changes during menstrual cycles and are indicative of hormone-dependent tumor cells.[19] If urinary calcium rises prior to the menses and falls following cessation of the menses, a beneficial effect, as measured by urinary calcium, will occur after castration. On the basis of urinary calcium change, he postulates that there are two types of cancer of the breast: (1) those that are hormone-dependent and are adversely influenced by estrogens, and (2) those that are hormone-independent and are unaffected by estrogens.

Estrogen has also been administered to patients with cancer of the breast and skeletal metastases in an attempt to select those who will benefit from castration: A rise in calcium excretion upon administration of estrogen indicates hormonal dependency and thus distinguishes those patients who will benefit from removal of estrogen sources. The authors in question report a case of a seventy-two year old woman who obtained a gratifying objective response from castration after previous estrogen stimulation had caused a rise in urinary calcium.[38] In our experience these methods for selecting patients for castration have been helpful chiefly in the

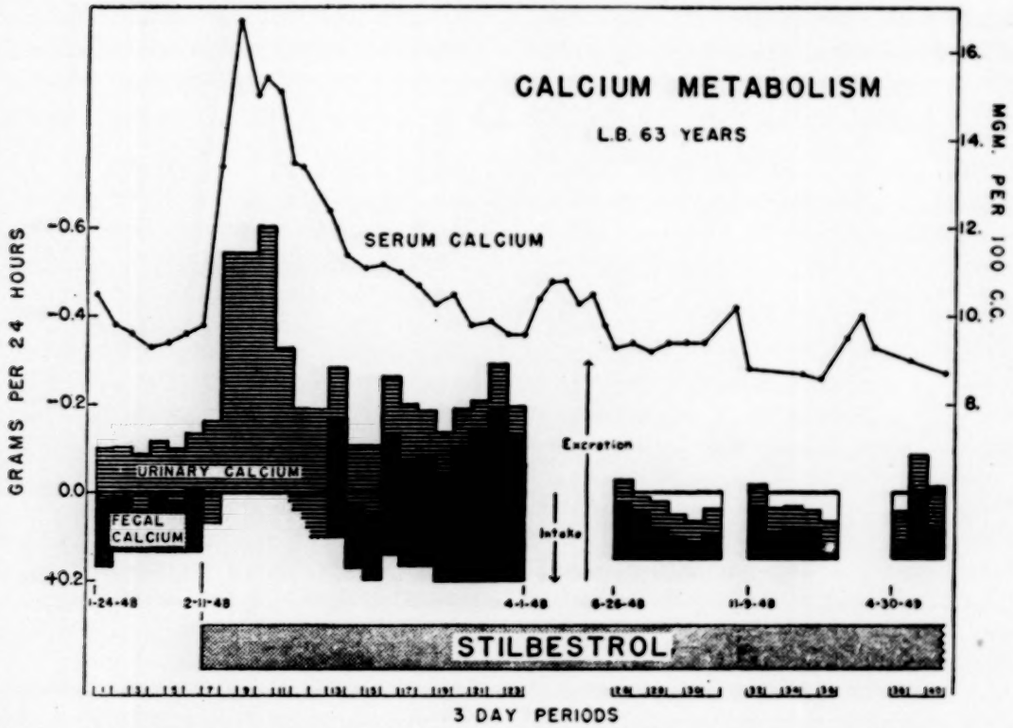


FIG. 2. From Kennedy et al.[14] with permission of the authors. Note the initial marked increase in serum and urinary calcium when the patient was given stilbestrol, eventually followed by a decrease on continued administration. Positive calcium balance eventually ensued, with x-ray evidence of recalcification of lesions in four months.

postmenopausal female. In the case of the estrogen stimulation test we have not had 100 per cent correlation with the results predicted on the basis of calcium excretion. A few of our patients have had increases in urinary calcium excretion following administration of estrogen and have shown no benefit whatsoever from castration. On the other hand, a few patients who have had no increases in calcium excretion at the dose range of 5 mg. of stilbestrol daily have received definite benefit from castration, with recalcification of their bony lesions. In addition, we have encountered two patients (Fig. 2) who have demonstrated an initial increase in serum and urinary calcium but have received ultimate benefit from continued administration of stilbestrol. Thus the initial effect may not in all cases predict future benefit. The precise effect of estrogens on bone metabolism in control subjects is not known, but in those patients who have postmenopausal osteoporosis a slight decrease in urinary calcium usually occurs, which in most cases is interpreted as repair of osteoporosis.[15] In such patients decreases in calcium excretion cannot be interpreted as complete evidence of beneficial antitumor effect. Increases in calcium excretion following administration of estrogen in mammary carcinoma are most probably associated with an increased growth rate of the tumor cells. It is also possible, however, that necrosis of tumor cells within the bone may occur, similar to the necrosis produced in soft tissues.[41]

Androgens. Early observations by Adair and others that administration of androgen in mammary carcinoma may frequently cause exacerbation of the disease, as manifested by hypercalcemia and hypercalciuria, have been confirmed by many investigators.[24–26,42] Indeed, in spite of marked symptomatic relief obtained with androgen therapy large increases in urinary calcium excretion and rapid dissolution of the bones, as shown by x-ray, can occur.[39,40] In most of the carefully studied cases in which androgen therapy has been continued no reversal of hypercalcemia or hypercalcuria took place.[8] The cause of the hypercalciuria and hypercalcemia induced by androgens is not known. Recent evidence has demonstrated the conversion of testosterone to estradiol by human tissue

and it is possible that such a conversion could cause an increased growth rate of estrogen-dependent cells, with resultant dissolution of bone.[43] This does not resolve the fact, however, that in about 20 per cent of metastatic mammary cancers androgens produce a beneficial recalcification of osteolytic lesions.[39,40] In some cases early increase in bone pain, nausea, vomiting and fever may augur a future beneficial effect of androgens; an initial increase in symptoms after administration of androgens may be only temporary and followed by a favorable host response and an osteoblastic reaction.

Cortisone. The beneficial effects of cortisone in carcinoma of the breast have been well documented by many authors.[44,45] In many such cases cortisone has produced a lowering of the serum and urinary calcium. In a very few of these cases recalcification of the bones has occurred. We are unable to explain completely this effect of cortisone. Cortisone may act by inhibition of ACTH, with a resultant decreased output of sex steroids by the adrenal gland and thus decreased growth rate of estrogen-dependent mammary carcinoma cells. Many other unknown factors may be involved, however.

Ablative Therapy. Castration and adrenalectomy may exert their beneficial effects upon calcium metabolism in neoplastic disease by removal of major estrogen sources which stimulate the tumor cells, thus tilting the dynamic tumor-host relationship in favor of the host. Hypophysectomy may benefit by removing trophic stimulation of the adrenals and ovaries, with resultant decrease in estrogen levels. In addition to the removal of gonadotropins, hypophysectomy removes thyrotropin and somatotropin. Both of these latter hormones may cause increases in calcium excretion; thus, to judge the effect of hypophysectomy by decrease in urinary calcium may be hazardous. In two patients, one reported by Pearson and the other by Jessiman administration of growth hormone to hypophysectomized patients with cancer of the breast resulted in increased calcium excretion.[46,47] Since increased calcium excretion occurs in acromegaly, it is difficult to interpret these data in respect to the mechanisms involved.[48]

SUMMARY AND CONCLUSIONS

The various factors governing the presence of metastatic cancer in bone are discussed. The reasons for the high incidence of osseous metastases seem to be related to the vasculature and fertile soil afforded by the skeletal system. The reasons for the various types of host reaction in bone are not altogether clear. They are probably related to the growth rate of the tumor cells and their individual biochemical characteristics.

The dynamic equilibrium that exists between bone dissolution and bone production in metastatic mammary carcinoma is subject to spontaneous changes, at times in favor of the tumor cells and at times in favor of the host. The development of hypercalcemia and/or hypercalciuria is usually accompanied by increased growth rate of tumor cells, with resultant destruction of bone and possibly of the tumor cells themselves.

The magnitude of calcium excretion is a guide to therapy but offers a gross and not unequivocal prediction of future benefit. The multiplicity of factors, both known and unknown, governing calcium excretion makes its use as a sole measure of objective effect unwise, and other parameters of antitumor effect should be used conjointly.

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Extirpative Endocrine Therapy for Advanced Cancer of the Breast*

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ALTERATIONS of hormonal factors in patients with cancer of the breast have significantly influenced the course of mammary cancer. Regressions of metastatic cancer of the breast or temporary cessation of growth as well as acceleration of tumor growth have been demonstrated upon administration or deprivation of various endocrine agents. Although the precise mechanisms of these agents cannot be defined observations suggest that the capacity of the hormonal factors to affect the growth of cancer of the breast is governed by the current endocrinologic status of the host. This is dependent in part on the function of the ovaries, adrenal glands and hypophysis. Observations have suggested that each of these glands is capable of producing agents favorable to the growth of cancer. Attempts consequently have been made to destroy or inhibit the function of these endocrine organs by radiation therapy, chemotherapeutic technics and surgical removal. This discussion will consider specifically the role of extirpation of the ovaries, adrenals and pituitary.

CASTRATION

A wide disagreement exists concerning the role of castration in the management of cancer of the breast and the optimum time for its performance. In 1889 Schinzinger proposed as a rational procedure surgical castration (ovariectomy) as a possible therapeutic approach to cancer of the breast.[1] This method of treatment was first employed by Beatson who in 1896 reported improvement following castration in inoperable cases.[2] This observation has been confirmed by many investigators.[3–6] Lett in 1905[6] collected ninety-nine patients treated by ovariectomy and noted marked improvement in 23 per cent of the patients and a distinct though less marked benefit in 13 per cent. Thereafter the reports of ovariectomy comprised only small numbers of cases because of the development of ovarian radiation.

Loeb[7] in 1913 reported that ovariectomy radically reduced the incidence of mammary tumors in mice. These findings established an experimental background of a relationship between mammary cancer and ovarian hormones. Castration has since become an accepted treatment for advanced cancer of the breast.

Therapeutic Castration. Castration is primarily of value as a palliative procedure in patients with advanced primary, recurrent or distant metastatic cancer of the breast. The beneficial effects are essentially confined to premenopausal women, though occasionally castration is of value a few years after spontaneous cessation of the menses when there is evidence of residual ovarian activity.[8] Effective ovarian radiation or ovariectomy may result in relief of symptoms (relief of pain, rehabilitation, increase in appetite and weight gain), objective regression of soft tissue lesions and calcifications of osseous lesions.[8,9] Neither the histologic picture of the cancer nor the clinical manifestations of the disease have been helpful in predicting a favorable response or in selecting the patient for castration. Suggestive evidence that castration may be of value is the patient with osseous metastases with exacerbation of bone pain in the premenstrual period, apparently due to estrogen stimulation of the tumor.

The data indicate that from 20 to 50 per cent of patients with advanced cancer of the breast obtain palliative benefit from castration. The average duration of such improvement is ten months with a range of three months to five years.

Halberstaedter and Hochman report improvement in 56 per cent of sixty cases castrated by ovarian radiation, though these observations include subjective (symptomatic) and objective

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responses.[10] Eight of the sixty patients had prophylactic castration. Of fifty-two patients, 50 per cent demonstrated subjective or objective improvement. Adair castrated 335 women, 15 per cent survived more than two years after the appearance of metastases.[11] Treves reported a series of 191 patients who had undergone ovariectomy.[12] Of these, 151 were in the premenopausal age and forty postmenopausal. An operative mortality of 2.5 per cent was recorded in each group. Objective improvement occurred in 43.7 per cent of the premenstrual group. The postmenopausal group had improvement in 18 per cent. Of these, however, five of the seven patients improved had had previous radiation therapy to the ovaries. Only one patient was more than five years postmenopausal.

Technic of Castration. The potential effects of castration have been confused by the methods available for ablation of the ovaries. Both ovariectomy and radiation of the ovaries have been employed. Surgery essentially guarantees permanent eradication of ovarian hormone production and ovulation. The efficacy of radiation in these effects is less certain and does not permit a critical analysis of the completeness of suppression of gonadal function. The development of amenorrhea and of menopausal symptoms is not a sufficient indication of the completeness of ovarian suppression. Studies of urinary gonadotropins, estrogen excretion and vaginal smears after ovarian radiation reveal considerable fluctuation, as contrasted to more constant levels after ovariectomy.[13] Even though ovarian activity appears to be completely suppressed following radiation, functional recovery of the ovaries may occur with the reappearance of menses. It is clear that failure to suppress ovarian function completely and permanently by radiation is due in part to insufficient dosage. The so-called "sterilizing" dose is inadequate. However, an adequate radiation dosage may be as efficacious as ovariectomy. When radiation is employed a dose of 1,200 to 1,500 r delivered as a tissue dose to the ovaries within a ten day period should be attained. Ovarian destruction can be judged by serial studies of the vaginal smear. The effective dose level appears to be higher in younger women because of greater ovarian activity.[8]

Suppression of ovarian function does not occur before a minimum of six to eight weeks after the initiation of radiation. If a rapid effect is necessary because of acute or distressing complications (hypercalcemia, liver involvement, brain metastases), ovariectomy is undoubtedly preferable. In some instances the patient may be too ill to tolerate anesthesia and a surgical procedure. In these instances concomitant radiation therapy and androgen hormone therapy may hasten the effect of radiation suppression of ovarian function.

The earlier studies on the effectiveness of ovarian irradiation in cancer of the breast need reevaluation because of the inadequate dosages frequently employed. That this is recognized is evidenced by recent trends toward the delivery of larger and more efficient doses of radiation. The present trend is towards ovariectomy for younger women, reserving radiation primarily for women in the forties when ovarian function is already declining.[8]

Following castration of young premenopausal women severe menopausal symptoms may occur. The usual management of this syndrome is not advised under these special circumstances. Since one of the prime purposes of ovarian ablation is the removal of estrogenic hormones, such agents are contraindicated as treatment of the menopausal symptoms. Androgenic hormones are also not recommended since it has been established that androgenic hormones are in part converted to estrogenic hormones[14] and also have been reported to accelerate the growth of cancer of the breast in 10 per cent of patients with osseous metastases.[15] When necessary, management of the menopausal syndrome in this instance consists primarily of sedation.

Mechanism of Action of Castration. The benefits of castration appear to occur primarily from estrogen deprivation. It has also been suggested that this results in a relative increase in androgenic or other hormonal activity.[8] Estrogens administered in the presence of active ovarian function may sometimes accelerate the growth of cancer of the breast.[16] Patients who responded favorably to castration have demonstrated exacerbation of the disease upon administration of small doses of estrogens.[17] On the other hand, intensified growth of cancer of the breast in premenopausal women has been observed, although rarely, with massive doses of estrogen which produce amenorrhea. In fact at dose levels of 1,000 mg. of stilbestrol daily regressions of tumor masses in a few patients have occurred.[18] These findings suggest that inhibition of pituitary growth hormone or tropic factors may play a role in control of the growth rate of cancer of the

breast. Most data suggest that the beneficial effects of castration are primarily due to removal of ovarian hormones (chiefly estrogens). Such cancers of the breast are referred to as ovarian-dependent tumors; ovarian non-dependent tumors being those not responding to castration.

Cancers of the breast showing profound regression after initial successful castration invariably undergo reactivation. This may be due to adaptations of the more resistant cells to an environment initially rendered unfavorable to tumor growth or to the endogenous production of estrogens from other sources. Postmortem examination of castrated patients revealed enlargement of the pituitary and adrenal glands. An increase of pituitary and/or adrenal hormones may exert a further effect which serves to reactivate the growth of the tumor.

Prophylactic Castration. There is widespread disagreement as to whether prophylactic castration increases the curability rate of patients in whom radical mastectomy is performed for a cancer confined to the breast or regional lymph nodes. Generally it appears that prophylactic castration does not increase the curability rate. Others strongly advocate castration as a preventive measure. The poor results of therapy in premenopausal patients, the promotion by pregnancy and lactation of growth of cancer of the breast, and the stimulating effect of endogenous estrogenic hormones are cited as reasons for recommending prophylactic castration.

The problem is two-fold: does prophylactic castration increase the period before the occurrence of metastases, and does it increase total survival time? The primary difficulty in evaluating this problem is the lack of comparable cases in a series of prophylactic castrations, therapeutic castrations and those not castrated. Furthermore, the number of cases in most series reported has been small.

Horsley states that in a series of thirty-nine premenopausal women treated by simultaneous radical mastectomy and surgical castration the five year "cure rate" was 76.9 per cent.[19] Sicard reported fifty-five women prophylactically castrated by surgery or x-ray.[20] There was no recurrence in six months to three years after radical mastectomy in forty-one patients. In view of the short follow-up period these figures are of little value.

Smith reported sixty patients castrated prophylactically by surgery.[21] Higher rates of survival were recorded among the castrates, the most striking difference occurring in the group with axillary metastases. The difference was not significant in these with negative axillary nodes. The same investigator analyzed forty-one patients who had received radiation castration. In twenty with axillary nodes the five year survival was 40 per cent, compared to 31 per cent in the control non-castrated group. This was inferior to the 74 per cent survival in the twenty-three surgically castrated patients. At ten and fifteen years after mastectomy the survival rates were the same as in the surgical group. The few cases in this series again do not permit a definite conclusion. There have been no significant reports dealing specifically with the results of prophylactic ovarian radiation.

Treves collected 116 patients who had had prophylactic castration.[12] Of these seventy-nine had been subjected to radiation castration and thirty-seven to ovariectomy. These were compared with 2,893 cases of radical mastectomy without other treatment. The report comprised five and ten year survival rates of patients free of clinical disease. In the non-castrated group the five year survival was 54.4 per cent. Of the entire group of prophylactically castrated patients, 63 per cent survived five years without clinical disease. Of the patients treated with radiation castration 54 per cent survived five years as compared with 81 per cent of the patients treated by ovariectomy. These preliminary data suggest that prophylactic castration prolongs the period before the onset of metastases. Further, with the smaller surgical figures, ovariectomy was superior to radiation therapy. The total survival data have not been reported.

In summary, it would appear that prophylactic surgical castration has a significant effect in delaying the onset of metastatic disease. Further, in comparison with a non-castrated group survival time may be prolonged in patients with axillary metastases. However, no data compare the effect of prophylactic castration in terms of total survival time with an equivalent group of patients in whom therapeutic castration is postponed until metastases are manifest. The survival period of these two groups may be the same.

Since one must consider further hormonal therapy after the onset of metastases, it may be advantageous to be able to carry out castration as a therapeutic procedure in order to determine whether or not the tumor is an ovarian-dependent lesion. In this manner the decision regarding

further endocrine gland ablative procedures or other hormone therapy would be made less difficult. In view of the long-term concept of hormonal therapy and the paucity of data regarding prophylactic castration, dogmatic support of the value of prophylactic castration is not justified for the present.

BILATERAL ADRENALECTOMY

It has been proposed that an adrenal component sustains or propagates certain types of mammary cancer. In mice gonadectomy induced adrenal hypertrophy and later the formation of adrenal cortical tumors.[22] Pathologic examination of patients previously castrated revealed enlargement of the adrenal glands in some cases. It was postulated that these were a source of increased amounts of hormonal factors that stimulated the growth of cancer of the breast.

Women with cancer of the breast who have undergone ovariectomy continue to excrete significant amounts of estrogenic compounds in the urine.[23] It is clear that the adrenal glands are capable of secreting hormones that can sustain the growth of cancer of the breast. When cortisone was made available to maintain patients after bilateral adrenalectomy this procedure was employed in the treatment of human cancer of the breasts. Since cortisone suppressed adrenal function, it was a natural corollary that cortisone be used to produce "chemical adrenalectomy" in far advanced cancer of the breast. The objective results of this latter therapy have not been as striking as the operative procedures.

Operative Management. Various technics have been employed in bilateral adrenalectomy. Some investigators removed both adrenals in one operation, others performed total adrenalectomy in two stages two weeks apart, and still others favor combined bilateral ovariectomy and adrenalectomy. Combined therapy, however, increased the difficulty in evaluating the effect of adrenalectomy alone. The management by various investigators of the patient treated by adrenalectomy is similar. Preoperatively cortisone, 100 to 200 mg. a day for forty-eight hours, is given intramuscularly. On the day of operation this is supplemented by intravenous hydrocortisone. Postoperatively administration of cortisone is gradually reduced to a daily maintenance dose of 50 mg. This is supplemented by 0.1 mg. of fluorohydrocortisone for its salt-retaining effect, which substitutes for the added salt intake and administration of DOCA previously employed. The usual precautions to be observed in management of an Addisonian patient are followed.

Results. From the numerous reports of the effect of bilateral adrenalectomy for advanced cancer of the breast, a review of 400 cases culled from the literature has been made. There appeared to be a definite dissociation between subjective and objective improvement. Relief of pain and increased feeling of well-being occurred in approximately 65 per cent of the patients. Objective regressions occurred in 34 per cent. The operative mortality rate was 7 per cent. Huggins reported thirty-four adrenalectomies with objective regressions occurring in 41 per cent.[23] The initial operative mortality was 5 per cent but has recently been reduced to 1.4 per cent. In a series of thirty-eight cases of metastatic cancer of the breast in women previously castrated, bilateral adrenalectomy produced objective remissions in 45 per cent.[24] The same investigators in a later report of seventy patients (by Pearson) recorded remissions, including arrested disease, in 50 per cent.[25] If only objective regressions are recorded the regression rate was 41 per cent. Similar results are reported by Cade.[27] It would appear that the rate of regression after bilateral adrenalectomy is similar to that following ovariectomy.

Huggins reported sixty-one patients with combined adrenalectomy and ovariectomy.[23] Of these 41 per cent had objective regressions. Since this figure is identical with that of the series of patients treated by adrenalectomy alone, there would appear to be no advantage in carrying out adrenalectomy in a premenopausal woman who had not previously been castrated.

The quality and type of tumor regressions have been similar to those recorded with castration and other hormone therapy. Calcification of osteolytic lesions, disappearance of skin nodules and lymph nodes, disappearance of pulmonary lesions and effusions, and decrease in primary lesions have been recorded. Patients with hepatic metastases have not done well. The mean duration of regression has been approximately nine months,[24] although remissions of more than two years have occurred.

Mechanism of Regressions. The benefits of adrenalectomy in women with advanced cancer of the breast are considered to be due primarily to the removal of another source of endogenous estrogenic hormone. It would appear, therefore, that cancer of the breast dependent on ovarian hormones should respond favorably to adrenal-

ectomy. The available data substantiate this. Patients who obtain a beneficial response from castration usually benefit a second time from adrenalectomy.[24] Patients failing to benefit from oophorectomy also fail to respond to adrenalectomy. Huggins, however, has reported significant regression of mammary cancer in patients who did not respond to castration or other hormone therapy.[23] Since androgenic hormones accelerate the growth rate of osseous metastases in some patients it is not inconceivable that the response after adrenalectomy is due in part to the removal of this source of endogenous androgenic hormone. Adrenalectomy may produce a general hormonal alteration of the tumor environment, disturbance of which may be responsible for some of the beneficial effects observed. Histologic examination of the primary tumor has not proved to be reliable in predicting the response to adrenalectomy.[23,26] Knowledge of the response of the premenopausal patient to castration provides the best criterion for selection of patients for adrenalectomy.

The failure of bilateral adrenalectomy to produce regressions in certain cases and relapse following remissions can be explained in part by incomplete removal of the adrenal glands or the presence of accessory adrenal tissue.

HYPOPHYSECTOMY

The pituitary gland apparently has an important role in the control of growth of cancer of the breast. In patients who have undergone castration for advanced cancer of the breast, an increase in the size of the pituitary and adrenal glands was noted. This hypertrophy may represent the source of hormonal agents important in the exacerbation of the disease. Certainly specific pituitary factors are involved in acceleration or maintenance of tumor growth in cancer of the breast. Hypophysectomy in rats definitely retarded the growth of tumors.[28] On administration of growth hormone to rats there was an increased incidence of neoplasms.[29] Growth hormone appears to have a stimulating effect on tumor growth in man. The administration of growth hormone to patients with advanced cancer of the breast and cancer of the prostate has produced an apparent increase in the growth rate of the disease.[30,31]

It has been postulated that the ameliorative effects of administration of massive doses of sex hormones in patients with cancer of the breast may be due to depression of pituitary function.[32] Cancer of the breast has not been observed in association with Simmond's disease. Attempts to produce complete pituitary suppression by radiation having failed, total surgical hypophysectomy has been employed in an attempt to control metastatic cancer of the breast.

Operative Management. Preoperative management consists of the administration of 200 mg. of intramuscular cortisone daily for forty-eight hours. The morning of the operation an additional 100 mg. is given orally. The operation requires the skill of an experienced neurosurgeon. A craniotomy is performed. Peyton[33] carries out an excision of the anterior medial portion of the right frontal lobe, providing a wide exposure of the sella turcica. Other neurosurgeons have retracted the frontal lobe. This would appear to increase the possibility of postoperative cerebral edema and convulsions. The hypophyseal stalk is divided and the pituitary gland removed. Postoperatively, cortisone requirements are the same as after adrenalectomy. Thyroid, 120 mg., is given in addition after recovery from the operation. Diabetes insipidus occurs in approximately one-half of the patients. Half of these require nasal pitressin powder to regulate the excessive polyuria. This has not been a difficult problem. As a rule no salt-retaining hormone or additional salt in the diet is required by these patients unless tumor has invaded and destroyed the adrenal glands. The operative morbidity and mortality is comparable to that of bilateral adrenalectomy.

Results. The benefits from surgical hypophysectomy have been similar to those following ovariectomy or adrenalectomy. Calcification of osteolytic lesions, regression of primary lesions, disappearance of lymph nodes and skin nodules, decrease in size of pulmonary lesions and improvement of hepatic metastases have been reported. The experience with hypophysectomy to date is still small. Luft and Olivecrona have performed fifty operations for cancer of the breast.[34] Subjective and objective improvement occurred in twenty patients (40 per cent). This series was unselected. Pearson et al. reported seventy-four patients, in thirty-six of whom "remissions" occurred.[35] Of these twenty-eight had objective regressions (38 per cent) and eight had apparent arrest of the disease. Eleven patients of this series had previously had ovariectomy and bilateral adrenalectomy. Ten of these had regression following adrenalectomy. Four of this group responded to hypophysectomy. Kennedy et al. have studied twenty-

eight *selected* patients.[36] Objective regressions occurred in eighteen patients (64 per cent) and two additional patients had metabolic remissions. The average duration of regression in the latter two series was 7.2+ and 7.6+ months, respectively.

Mechanism of Effect of Hypophysectomy. Hypophysectomy provides another means of altering the metabolic status of the patient. Removal of the pituitary gland eliminates some of the stimulating factors of cancer of the breast. In the patient with intact ovaries or adrenal glands the benefit may be the result of suppression of these endocrine glands, comparable to their surgical ablation. In addition, removal of the pituitary eliminates growth hormone, which appears to regulate the growth of cancer of the breast. Recovery of function of pituitary remnants or accessory pharyngeal pituitary tissue may account for the eventual reactivation of cancer of the breast after hypophysectomy.

A careful selection of patients for hypophysectomy is required. It would appear that a premenopausal patient with advanced cancer of the breast responding to therapeutic castration will subsequently respond to hypophysectomy. Postmenopausal women who responded to estrogenic or androgenic hormone therapy will probably undergo a further regression after hypophysectomy. Further experience will define more critically the role of hypophysectomy in the treatment of advanced cancer of the breast.

CONCLUSIONS

Alteration of the hormonal status of women with advanced cancer of the breast has an influence upon this disease. The maintenance and growth of the tumor is dependent in part upon hormonal factors of the ovaries, adrenal glands and pituitary gland. Extirpation of one or all of these endocrine organs will temporarily inhibit growth of the cancer in selected patients and may be successfully employed as therapy in the long-term treatment of cancer of the breast. No explanation is available for the failure of certain cancers of the breast to respond to such therapy, other than the surmise that such tumors are not dependent upon hormonal factors for growth.

There is no doubt that therapeutic castration in premenopausal women with metastatic cancer of the breast will produce a beneficial effect in up to 45 per cent of the patients treated. Such disease is referred to as ovarian-dependent or hormone-sensitive cancer of the breast. The remaining patients as a rule do not respond well to other forms of hormone therapy. The role of prophylactic castration at the time of radical mastectomy is not as clearly defined. Prophylactic castration would appear to delay the time of onset of recurrence of the cancer. There are no data to suggest that this procedure increases the "cure rate" of cancer of the breast. Furthermore, no adequate report is available that affords valid comparison of the total survival time of patients who have undergone prophylactic castration with those who have had a therapeutic castration when metastases were already clinically manifest. Such data are urgently needed. To date, many investigators employ therapeutic castration, since the response of the cancer provides the knowledge necessary for the subsequent decisions of hormonal therapy, ablative or administered. Most patients who respond favorably to therapeutic castration will subsequently improve following adrenalectomy or hypophysectomy.

Bilateral adrenalectomy in patients with advanced cancer of the breast has resulted in objective improvement in 30 to 45 per cent of the patients so treated. Patients who previously responded to therapeutic castration will most likely respond to adrenalectomy. The present status of this procedure is ambiguous since the improvement is no greater than with hypophysectomy, and management of the patient treated by adrenalectomy is difficult.

The role of hypophysectomy in the treatment of advanced cancer of the breast is in the process of being defined. Again, premenopausal women responding to therapeutic castration and postmenopausal women demonstrating improvement from estrogen or androgen administration appear to respond favorably to hypophysectomy. Whether hypophysectomy alone can produce an effect equal to the sum of ovariectomy, adrenalectomy and hypophysectomy remains to be determined. At present hypophysectomy provides a further investigative opportunity to determine the role of hormones in cancer of the breast.

Alterations in the growth of cancer of the breast may occur spontaneously and account for the wide variations in the course of untreated cancer of the breast. Destruction by cancer of the ovaries, adrenal glands and pituitary gland have all been demonstrated with cancer of the breast. Such autogenous ablation of these endocrine organs may explain some of the spontaneous variations in the growth of cancer of the breast.

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Hypophysectomy in the Treatment of Malignant Tumors*

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THE effect of hypophysectomy on the course of certain malignant diseases, especially metastatic cancer of the breast, has been under study in our departments during the past several years. Preliminary results have already been summarized.[1–3] In the present report the results obtained so far by us and by other groups are presented.

Operative Technic. The technic used was described in detail in 1953.[2] In brief, after exposure of the pituitary region by a frontotemporal approach the pituitary stalk is clipped and divided. The diaphragm of the sella is incised and the gland is then mobilized by blunt dissection and removed, usually in pieces, with rongeurs and spoons. After controlling hemorrhage the walls of the sella are cauterized with Zenker's solution. During the past year sodium hydroxide also has been used as a cauterizing agent.

Management of the Patients. The preoperative care of the patients has changed during these years, some patients have been operated upon without any substitution therapy at all. The schedule followed at present consists of the administration of cortisone† in two 100 mg. doses, one on the evening of the day before operation and the other in the morning of the day of operation. Postoperatively, cortisone is given in doses of 50 mg. every four hours during the first twenty-four hours, then in decreasing doses to the maintenance dose of 25 to 50 mg. per day on the eighth to fifteenth day. Administration of parenteral fluids and electrolytes is adjusted to individual needs during the first forty-eight hours. By the third day the patients are usually taking fluid and food by mouth.

In the case of patients who have previously undergone adrenalectomy, cortisone is given before operation as described, together with two 10 mg. doses of desoxycorticosterone acetate (DCA). During the operation hydrocortisone acetate, 100 mg. in one liter of isotonic glucose, is given by intravenous drip. The hydrocortisone drip is continued postoperatively during the first twenty-four hours, the patient receives in all about 200 mg. of hydrocortisone. On the second day cortisone therapy, 200 to 300 mg. per day is begun; these doses are gradually decreased to the daily maintenance dose of 50 to 75 mg.

Thyroid replacement therapy is started during the second to third postoperative month after tests of thyroid function have been performed. The maintenance dose has been 50 to 100 micrograms of thyroxin.

Case Material. Seventy-five patients with malignancy have been subjected to hypophysectomy (as of January 1, 1956).‡ The diagnosis in these patients was as follows:

Cancer of the female breast	55
Previous oophorectomy and adrenalectomy	3
Cancer of the male breast	2
Cancer of the prostate	10
Chorionic epithelioma	2
Cancer of the ovary	2
Cancer of the adrenal gland	1
Malignant melanoma	3
Total	75

The effect of hypophysectomy on the course of the disease was evaluated on the basis of objective criteria, and was classified as: regression, arrest and no response. The response was classified as: *regression* when there was a decrease in visible (by inspection or on x-ray) or palpable

† The generous supply of steroid hormone preparations by Ciba Produkter A.B., Stockholm, is gratefully acknowledged.

‡ Five patients with cancer of the breast operated on by other surgeons and presented in a previous report[3] are not included.

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TABLE I—EXPERIENCES WITH HYPOPHYSECTOMY FOR CANCER

Disease	References									Total
	Present Study	4 and 5	6	7	8	9	10	11	12 to 17	
Cancer of the female breast										
1. No adrenalectomy										
Evaluated	41	56	(22)*	18	10	13	(25)	(6)	6	197
Remissions	22	32	15	12	8	9?	7	2	3	110
2. Previously adrenalectomized and oophorectomized										
Evaluated	..	11	.....	..	..	....	.....	....	..	11
Remissions	..	5	.....	..	..	....	.....	....	..	5
Cancer of the male breast										
Evaluated	2	1	.....	..	..	1	.....	....	..	4
Remissions	2	1	.....	..	..	1	.....	....	..	4
Cancer of the prostate										
Evaluated	7	(4)	.....	..	..	....	.....	....	5	16
Remissions	5	1	.....	..	..	....	.....	....	2	8
Malignant melanoma										
Operated	3	4	.....	..	..	....	4	....	1	12
Remissions	0	0	.....	..	..	....	0	....	0	0
Chorionic epithelioma										
Operated	2	2	.....	..	..	....	.....	....	..	4
Remissions	1	0	.....	..	..	....	.....	....	..	1
Cancer of the ovary										
Operated	2	....	.....	..	..	....	.....	....	..	2
Remissions	0	....	.....	..	..	....	.....	....	..	0
Cancer of the adrenal										
Operated	1	....	.....	..	..	....	.....	....	1	2
Remissions	0	....	.....	..	..	....	.....	....	0	0
Thyroid carcinoma										
Operated	..	1	.....	..	..	....	.....	....	..	1
Remissions	..	0	.....	..	..	....	.....	....	..	0
Reticulum cell sarcoma										
Operated	..	1	.....	..	..	....	.....	....	..	1
Remissions	..	0	.....	..	..	....	.....	....	..	0
Cancer of the uterus										
Operated	..	....	.....	..	..	....	3	....	..	3
Remissions	..	....	.....	..	..	....	0	....	..	0
Sarcoma of the breast										
Operated	..	....	.....	..	..	....	1	....	..	1
Remissions	..	....	.....	..	..	....	0	....	..	0

* The figures within brackets denote that all patients operated upon were considered.

metastases, or increased density of previously osteolytic bone metastases, without progression of any old metastases or appearance of any new metastases; *arrest* when no progression of any metastases could be detected and new metastases did not appear; *negative* (no response) when the metastases continued to grow or new metastases appeared. Remission of the disease by hypophysectomy (regression or arrest) was always accompanied by pronounced subjective improvement. In some patients in whom the response was objectively classified as negative there was a more or less

pronounced subjective improvement for rather short periods of time, up to five months. The remission was considered ended when cancer growth recurred, as judged by reappearance of pain and/or progression of old metastases or appearance of new ones.

The evaluation of the results is as of June 30, 1956, thus permitting a minimum time of observation of six months.

RESULTS

The results obtained by hypophysectomy are presented in Table I.

Cancer of the Female Breast. Up to June, 1954, hypophysectomy was performed on all patients with metastatic cancer of the breast referred to us. Later on, patients with extensive liver or brain metastases were rejected. The response to hypophysectomy in the fifty-two patients who had not undergone previous adrenalectomy was as follows:

Operated		52
Not evaluated		11
Operative deaths	3	
Postoperative complications	2	
No follow-up	3	
Evaluation not possible	3	
Evaluated		41
Remission		22
Arrest	6	
Regression	16	
No response		19
Dead within 2 months from progression of cancer	3	

Three of the patients died from causes directly connected with the operation. The two fatal postoperative complications encountered were pulmonary embolism and bronchopneumonia. No follow-up studies were available in one patient living in a distant country. A second patient died from cardiac failure due to coronary thrombosis two months after hypophysectomy; no signs of progression of the cancer were observed postoperatively in this case. A third patient died in another hospital of adrenocortical insufficiency during the second postoperative month.

The pertinent data in the three cases in which evaluation was not possible follow:

First case: In a forty-three year old woman hypophysectomy was performed one week after removal of a cerebellar metastasis, no other metastases being discovered. There was recurrence of the cerebellar metastasis seventeen months later; the patient died twenty-two months after hypophysectomy. No other macroscopic metastases were found at autopsy.

Second case: A woman seventy-six years old received androgenic hormones after hypophysectomy. There was subjective improvement for more than seven months and probably increased density of skeletal metastases. She died ten months after the operation. Administration of androgens during the immediate preoperative period was without effect.

Third case: This was a forty-eight year old woman who received one implantation of 500 mg. of testosterone propionate in the second postoperative month. There was remarkable subjective improvement lasting twenty-six months. Skeletal x-rays one year postoperatively demonstrated extensive calcification of previously osteoplastic and osteolytic metastases; however, one year later new osteolytic metastatic lesions were visible. She died thirty-three months after hypophysectomy, of progression of her cancer.

Data on the forty-one cases in which results were evaluated are presented in Table II. In twenty-two of these (54 per cent), hypophysectomy induced a remission, regression in sixteen and arrest in six. In nineteen cases no response was observed. Three of the latter patients died of cancer within the first two postoperative months; they all had extensive metastases, involving the liver in three and the brain in two. The survival time was so short in these cases that there was probably no time for any response to the operation.

The *duration of remission* was as follows:

	No. Cases	Range (months)	Mean (months)	Still in Remission (no. cases)
All remissions	22	4–32	14.1+	6
Arrest	6	4–12	7.7+	1
Regression	16	>6–32	16.4+	5
Cases operated before July 1954	14	6–32	16.5+	1

In the group of patients with remission, and with a postoperative observation period of at least two years, only one is still in remission. The results in this group indicate that the duration of remission induced by hypophysectomy was approximately seventeen months.

The significance of certain factors on the re-

sponse to hypophysectomy will now be considered. Because of the limited number of cases only tentative conclusions are possible.

The relation between *menstruation* and response to hypophysectomy was as follows:

	Operated	Remission	No Response
Premenopausal	13	9	4
Artificial menopause (hormonal, x-ray, surgical)	10	6	4
Postmenopausal	16	6	10
5–10 years	8	2	6
>10 years	6	1	5
Unknown (extirpation of uterus)	2	1	1

These findings suggest that in postmenopausal women the chances of a beneficial effect of hypophysectomy are less the longer the duration of the postmenopausal period.

The effect of the *age* of the patients at operation on the response to hypophysectomy was as follows:

Age (years)	Operated	Remission	No Response
31–40	7	5	2
41–50	17	8	9
51–60	12	9	3
61–70	5	1	4

It thus seems that women more than sixty years of age probably will not respond to hypophysectomy. In this age group all patients were postmenopausal for ten years or longer.

The effect of the *duration* of the disease (time interval between first sign of cancer of the breast and hypophysectomy) was:

Duration (months)	Operated	Remission	No Response
–24	11	4	7
25–48	11	6	5
49–72	12	7	5
73–	7	5	2

Eight of the forty-one patients in whom the results could be evaluated had brain and/or extensive liver metastases. Remission was obtained only in two of these. (Table I.)

As to the relation between the effect of *previous hormonal treatment* and the response to hypophysectomy, no data can be given. Such treatment had been tried in many cases but in most instances together with irradiation.

In twelve patients (Nos. 2,3,4,6,16,17,18,25, 28,32,34,46) androgens, usually in a dose of 50 mg. per day, were given when remission ended or when no remission was obtained. This treatment did not influence the course of the disease in any case, neither did it cause any remarkable subjective improvement.

Three patients who had undergone previous oophorectomy and adrenalectomy were subjected to hypophysectomy.* All three had very extensive metastases including involvement of the liver and died of cancer thirteen, twenty-two and 40 days after the operation. These data do not permit evaluation.

Cancer of the Male Breast. Hypophysectomy was performed on two patients with metastatic cancer of the breast. Regression was obtained in both.

First case: The patient was born in 1888; cancer was diagnosed in 1945. In December, 1952, he received treatment with 200 mg. of stilbestrol daily which worsened his condition. At hypophysectomy in April, 1953, the patient presented lymph gland and very extensive lung metastases. He died thirty-five months later of cardiac failure due to pulmonary fibrosis. No macroscopic metastatic lesions were observed at autopsy.

Second case: A fifty-nine year old man with breast cancer since 1948. After hypophysectomy there was regression of skeletal and extensive pulmonary metastases. He is still in remission thirty-two months postoperatively.

Cancer of the Prostate. Of the ten patients operated on, three died shortly postoperatively from heart failure, bronchopneumonia and cerebral thrombosis. The first two were sixty-six and sixty-seven years old and very poor operative risks. The pertinent data in the remaining seven cases are summarized in Table III.

Remission of the disease was observed in five of these seven cases, arrest in three and regression in two. In two of the cases the arrest was brief,

* The authors are indebted to Drs. John Hellström and Curt Frankson for referring these patients to us.

TABLE II—RESULTS OF HYPOPHYSECTOMY IN 41 PATIENTS WITH CANCER OF BREAST

Case No.	Born	First Symptom (date)	State of Menstrual Cycle	Metastases at Hypophysectomy						Date of Hypophysectomy	Effect	Duration of Remission (months)	Survival (months)	Remarks
				Soft Tissues	Lungs and/or Pleura	Skeleton	Brain	Liver	Eyes					
1	1902	June, 1945	X-ray castration, January, 1948	+	...	..	..	..	..	1/29/52	Regression	19	48	.....
2	1891	May, 1946	Menopause, 1940	+	...	+	..	..	..	2/14/52	No response	....	18	.....
3	1906	July, 1948	Menopause, 1951 (hormonal)	+	+	..	..	+	..	4/18/52	No response	....	1	.....
4	1888	October, 1943	Menopause before 1933	+	+	+	..	..	..	5/27/52	No response	....	11	.....
5	1909	April, 1950	Normal	..	+	+	+	+	+	9/18/52	No response	....	2	.....
6	1904	March, 1952	Menopause, 1951	+	...	..	+	..	..	9/22/52	No response	....	9	.....
7	1906	May, 1950	Irregular	+	...	+	..	..	..	10/14/52	Regression	15	23	.....
8	1916	February, 1951	Normal	+	+	+	..	..	..	10/22/52	Regression	9	10	Died of adrenal insufficiency
9	1888	November, 1948	Menopause, 1943	..	+?	+	..	..	..	2/13/53	No response	....	5	.....
10	1913	December, 1950	Normal	+	...	+	..	..	..	3/25/53	Regression	13	21	.....
11	1894	April, 1950	Menopause, 1944	+	...	+	..	..	..	4/17/53	No response	....	10	Subjective improvement five months
12	1896	September, 1950	Menopause, 1945	+	...	..	..	..	..	4/22/53	Regression	23	33	Died of erysipelas
13	1914	April, 1951	Amenorrhea, October, 1952 (hormonal)	..	...	+	+	..	..	5/6/53	No response	....	4	.....
14	1899	June, 1948	Menopause, 1949	+	...	+	..	..	..	5/7/53	Regression	32	38+	Alive, relapse
15	1902	July, 1950	Irregular	..	+	+	..	..	+	5/8/53	Regression	15	22	.....
16	1903	October, 1947	Menopause, 1948	+	...	+	..	..	..	6/4/53	No response	....	9	Subjective improvement three months
17	1905	November, 1951	Normal	..	+	+	+	+	..	6/8/53	No response	....	2	.....
18	1910	September, 1952	Normal	+	+	..	..	..	..	8/28/53	No response	....	3	.....
19	1908	September, 1951	Normal	+	+	..	..	..	..	9/4/53	No response	....	3	Cause of death unknown
20	1901	November, 1951	Normal	+	+	+	..	..	..	10/15/53	Arrest	7	9	.....
21	1908	December, 1948	Normal	+	...	+	..	..	..	11/16/53	Regression	31+	31+	Alive, in remission
22	1910	May, 1947	Normal	..	...	+	..	..	..	12/17/53	Regression	25	30+	Alive, relapse

TABLE II (*Continued*)

Case No.	Born	First Symptom (date)	State of Menstrual Cycle	Metastases at Hypophysectomy						Date of Hypophysectomy	Effect	Duration of Remission (months)	Survival (months)	Remarks
				Soft Tissues	Lungs and/or Pleura	Skeleton	Brain	Liver	Eyes					
23	1894	June, 1949	Menopause, 1942	..	+	+	..	..	..	12/17/53	No response	....	7	Subjective improvement three to four months
24	1921	February, 1949	X-ray castration, February, 1953	..	+	+	..	..	..	2/24/54	Regression	15	18	.....
25	1902	January, 1950	Menopause, 1950	..	+	+	..	..	..	5/21/54	Arrest	12	25+	Alive, relapse
26	1913	March, 1949	Amenorrhea, November, 1953 (hormonal)	+	+	+	..	..	..	6/15/54	Arrest	9	17	.....
27	1903	May, 1953	X-ray castration, February, 1954	+	...	..	..	..	..	6/15/54	Arrest	6	9	.....
28	1924	June, 1953	X-ray castration, October, 1953	+	+	..	..	..	..	7/14/54	No response	....	9	.....
29	1906	February, 1946	Menopause, 1952	..	+	+	..	..	..	11/4/54	Regression	20+	20+	Alive, in remission
30	1907	April, 1946	Menopause, 1952	..	+	..	..	..	..	11/18/54	Regression	6+	6	Died after laparatomy while in remission
31	1921	March, 1953	Normal	..	+	+	..	+	..	12/6/54	Regression	11	13	.....
32	1904	January, 1949	Uterus extirpation, 1941	+	...	+	..	+	..	12/20/54	No response	....	8	.....
33	1892	December, 1953	Menopause, 1938	+	+	..	..	..	..	2/1/55	No response	....	8	.....
34	1913	June, 1952	X-ray castration, July, 1954	+	+	+	..	..	..	4/21/55	No response	....	12	.....
35	1910	April, 1955	Normal	+	...	+	..	..	..	6/22/55	Regression	12+	12+	Alive, in remission
36	1899	June, 1953	X-ray castration, June, 1953	+	...	..	..	..	..	6/29/55	No response	....	12+	Alive
37	1899	May, 1943	Menopause, 1952	+	...	+	..	..	..	9/12/55	No response	....	10+	Alive
38	1904	January, 1949	Surgical castration, July 1954	..	...	+	..	..	..	10/21/55	Regression	8+	8+	Alive, in remission
39	1917	February, 1950	X-ray castration, January, 1954	..	...	+	+	..	..	11/8/55	Regression	8+	8+	Alive in, remission
40	1890	October, 1949	Menopause, 1940	+	...	+	..	..	..	11/15/55	Arrest	8+	8+	Alive, in remission
41	1904	January, 1953	Uterus extirpation, 1942	+	+	..	..	..	..	12/18/55	Arrest	4	7+	Alive, relapse

TABLE III—RESULTS OF HYPOPHYSECTOMY IN 7 PATIENTS WITH PROSTATIC CANCER

Case No.	Born	First Symptom	Date of Operation	Previous Endocrine Treatment		Date of Hypophysectomy	Effect	Duration of Remission (months)	Survival (months)	Remarks
				Type	Effect					
1	1884	May 1946	May 1946 April 1950	Castration Stilbestrol (3 months)	Good None	4/9/52	Arrest	2	4	.....
2	1893	June 1951	.....	Castration and stilbestrol	Doubtful	1/12/53	Arrest	8+	8	Died of pyelonephritis (while in remission)
3	1892	1951	January 1953	Castration Stilbestrol (3 months)	Good Good	4/30/54	Regression	8	26+	Alive, relapse
4	1895	June 1952	.....	Stilbestrol (3 months)	None	4/18/54	Regression	24+	24+	Alive, in remission
5	1895	December 1952	December 1952	Castration	None	9/8/54	Arrest	3	?	Died in relapse
6	1886	1947	.....	Stilbestrol (4 months)	None	10/4/54	No effect	....	3	.....
7	1899	December 1952	.....	Stilbestrol (11 months)	Good	3/31/55	No effect	....	4	Subjective amelioration for two months

two and three months. It is of interest that remissions were obtained in two cases (Nos. 4 and 5) in which previous endocrine treatment was without effect.

Chorionic Epithelioma. Of the two patients who underwent hypophysectomy, in one regression was observed postoperatively. This case was presented *in extenso* previously.[2] The second patient was a very poor operative risk because of extensive pulmonary metastases; she died on the fifth postoperative day.

Other Malignancies. In two patients with widespread metastatic ovarian cancer and one with metastatic cancer of the adrenal cortex, hypophysectomy did not alter the course of the disease. Of the three patients with malignant melanoma, one died on the third postoperative day and the second three weeks after operation. In this latter case, the large cutaneous metastases changed markedly a few days before death; the previously nodular bluish infiltrations disintegrated and looked like large ecchymoses. The third patient with melanoma survived for three months without any appreciable change in the course of the disease.

Endocrine Functions after Hypophysectomy. In Table IV data on the functional status of the thyroid and adrenal glands after the operation in nineteen of the women with cancer of the breast are presented. The daily excretion of 17-ketosteroids* did not exceed 1.9 mg. when the patients were not given substitution therapy, and 3.5 mg. in the patients receiving cortisone, usually 25 mg. per day. In contrast, thyroid function as measured by radioiodine* was retained in at least nine of the nineteen cases (Nos. 7,12,17,21,22,25,31,34,41). The basal metabolic rate did not correlate well with the results of the radioiodine studies. These results demonstrate that, as judged by thyroid function, hypophysectomy was not complete in all cases.

The daily excretion of 17-ketosteroids and corticoids* in Cases 14 and 22 after discontinuation of cortisone substitution therapy is shown in Figure 1. Although in both cases hypophysectomy was incomplete, as judged by radioiodine studies (Table IV), no increase in the excretion of steroids was observed during this period. In Case 22, ACTH administered intravenously induced an appreciable increase in the excretion of corticosteroids; thus in this case at least the adrenals were able to respond to ACTH.

COMMENTS

It is generally accepted that estrogens and androgens are in many instances associated

* 17-ketosteroids were measured according to Westergaard[18] and corticosteroids according to Norymberski.[19] Radioiodine studies were performed according to Clark et al.[20] and Berson et al.[21]

with the growth of cancer of the breast and prostate in man. This view is based on the remissions obtained in such cases by sex hormone control, such as elimination of estrogens or androgens from the body. For such control, castration and/or adrenalectomy have been used with good results.[22–28] On the other hand, there is—in addition to experimental evidence—also clinical evidence which suggests that pituitary hormones influence the growth of these malignancies by routes other than by way of the steroid hormones. Thus administration of estrogens in women with cancer of the breast induces remission in 30% of postmenopausal women and even in some premenopausal women.[29,30]

For these reasons hypophysectomy is a rational approach in the treatment of metastatic cancer of breast and prostate in man. Complete removal of the pituitary tissue is followed by cessation of secretion of the pituitary hormones and, as a result, also of steroid hormones. Thus by a single operation complete control of pituitary and sex hormones is achieved.

As to the other malignancies for which hypophysectomy was tried, no clear rationale can be given; the operation was undertaken mostly for investigative purposes.

TABLE IV—EFFECTS OF HYPOPHYSECTOMY ON THYROID AND ADRENAL FUNCTION

Case No.	Urinary 17-ketosteroids (mg./24 hr.)	Basal Metabolic Rate (%)	Radioiodine				
			Thyroid Clearance (ml./min.)	24 Hr. Uptake (%)	Conversion Ratio (%)		PBI-131 (%) 48 Hr.
					24 Hr.	48 Hr.	
7	1.5	−17	14	43	..	..	....
12	1.3	−22	20	30	8	46	....
14	0.5	−20	<1	13	..	..	....
15	*1.6**	−6	<1	6	..	..	....
17	....	....	8	37	..	..	....
21	*2.5*	−25	6	29	..	..	....
22	1.3	−23	17	50	..	..	....
24	0.9	−23	0	1	..	..	....
25	1.1	−17	11	21	3	15	0.2
28	0	−16	3	2	..	..	....
29	*2.5*	−9	0	..	0	0	0
31	*1.7*	−22	8	12	..	..	....
34	1.4	−26	18	48	5	66	....
35	1.8	−14	0	10	0	0	....
37	*1.5*	−19	0	0	0	0	0
38	*5.2*	−31	0	10	2	10	0.01
39	*3.5*	−27	0	6	6	26	0.02
40	*1.8*	−22	0	0	0	0	0
41	....	−13	7	29	4	9	0.2

* Italicized figures represent measurements from patients receiving cortisone, 25 mg. per twenty-four hours.

The present results demonstrate that hypophysectomy may induce remission in metastatic cancer of the breast. The percentage of remissions so obtained was 54 per cent of the evaluated cases. The data in the literature* (Table 1) indicate that about 56 per cent of the evaluated cases responded favorably to hypophysectomy. This figure is higher than the percentage of remissions after adrenalectomy plus oophorectomy (45 per cent, see Pearson[4]). However, it cannot yet be stated with certainty that hypophysectomy induces remission in a higher percentage of cases than adrenalectomy or combined adrenalectomy and oophorectomy. The figures cited for both groups of results are based on data collected by different authors, and some groups of cases are selected ones. It is of special interest that Pearson et al.[4] reported remissions after hypophysectomy in patients who had undergone previous oophorectomy and adrenalectomy. These authors consider the possibility that this beneficial effect might depend on the elimination by hypophysectomy of steroid production in aberrant adrenocortical tissue. It seems probable how-

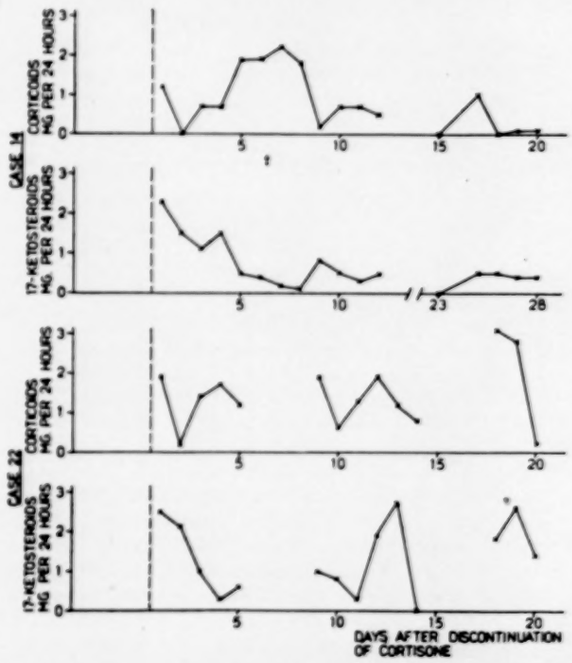


FIG. 1. Urinary excretion of 17-ketosteroids and corticoids in two incompletely hypophysectomized patients with cancer of the breast after discontinuation of cortisone substitution therapy.

* The results reported by some authors[31,32] could not be evaluated.

ever, that the cortisone substitution therapy customary after adrenalectomy would not permit hormone production in this aberrant tissue.

In the present series the remission induced by hypophysectomy lasted longer than that after oophorectomy and/or adrenalectomy; the mean

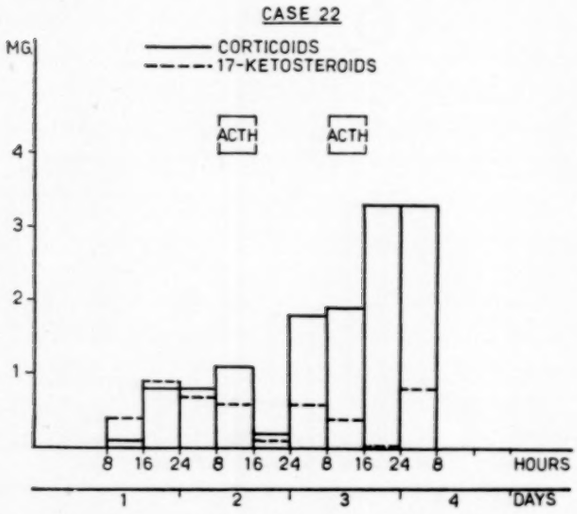


FIG. 2. Response to intravenous ACTH in an incompletely hypophysectomized patient (25 mg. of ACTH between 8 a.m. and 4 p.m. on the second and third days).

duration of remission was approximately seventeen months as compared to nine months.[4] Again, for the reasons already mentioned the available data cannot be taken as conclusive.

Our experience and that of other authors with other malignancies (Table I) is limited. Hypophysectomy has induced remissions in cancer of the prostate and probably in one case of chorionic epithelioma.

Previous to 1951 only isolated attempts to remove or destroy the hypophysis had been reported.[33–36] Since then hypophysectomy has been employed in several series of cases. (Table I.) Complete destruction of the hypophysis has been attempted by the following methods:

Surgical: Frontotemporal approach[2]
Frontal approach[12,37,8]
Transnasal approach[37]
Transantral approach[37,38]
Radiation: External[39]
Local application[31,40–47]
Electrocoagulation:[2,44,49]

In the present series hypophysectomy was incomplete in a significant number of cases, as judged by the radioiodine tests. Minute histologic examination of the sella turcica in twenty-six cases, by serial sectioning, showed that anatomically complete removal of the hypophysis had been accomplished only in a few instances, and that in most of the cases pituitary cells were present, usually in small amounts. Pearson et al.[5] found pituitary remnants in two of eleven cases in which serial sectioning was performed (for the other groups of cases in Table I no detailed data on the completeness of the operation are available). It is too early to determine which of the methods employed will give complete anatomic removal or destruction of the hypophysis in all or most of the cases.*

Different criteria are used to evaluate the completeness of hypophysectomy during life. It is obvious that persistence of measurable amounts of pituitary hormones and/or maintenance of pituitary-conditioned functions of peripheral endocrine glands excludes complete hypophysectomy.† Whether functionally complete hypophysectomy requires complete anatomic removal cannot be stated at present.

The important question whether or not complete hypophysectomy in all cases would give improved results in respect to percentage and duration of remission cannot be answered. We have observed remission in patients who were incompletely hypophysectomized (Nos. 7,12,21, 22,25,41 in Tables II and III) as judged by radioiodine tests, the last patient having been postmenopausal for ten years.

The finding in Case 22 that urinary excretion of steroids did not increase with time after discontinuance of cortisone administration (Fig. 1), although the adrenal cortex was able to respond to ACTH (Fig. 2), raises the question whether or not hypophysectomy incomplete with respect to thyroid function is functionally incomplete in respect to other pituitary hormones.

The important question, which patients with cancer of the breast or prostate may be expected to benefit by hypophysectomy, cannot yet be answered. In the case of cancer of the breast, it

* Tönnis et al.[51] discuss the possibility that extrasellar pituitary tissue might take over pituitary functions when the pituitary tissue in the sella has been destroyed. If this suggestion is correct complete hypophysectomy cannot be achieved by the procedure employed.

† The necessity for cortisone substitution therapy after hypophysectomy makes it difficult to evaluate adrenocortical function. Moreover, functional tests performed shortly after hypophysectomy might be misleading since the remaining pituitary tissue might not have had enough time to restore and/or increase its functional capacity.

seems at present that the course of the disease in patients with brain and/or extensive liver metastases, above sixty years of age (our data), and those who did not respond to other forms of endocrine treatment[5] most probably will not be altered by hypophysectomy.

The value of hypophysectomy in the treatment of malignancies and especially of metastatic cancer of the breast and prostate cannot be established before a large enough series of patients with anatomically complete hypophysectomy is available. The results obtained so far in metastatic cancer of the breast demonstrate that hypophysectomy is at least as good as other forms of endocrine treatment of this malignancy.

CONCLUSIONS

Hypophysectomy was performed in seventy-five patients with metastatic malignancies.

Remission was induced in twenty-two of forty-one cases of metastatic cancer of the breast in women, the mean duration of the remission being approximately seventeen months. From the data in literature it would appear that hypophysectomy induced remission in 110 of 197 such cases (56 per cent).

Remissions were obtained by this procedure in both of two men with metastatic cancer of the breast, in five of seven cases of metastatic cancer of the prostate, and apparently in one of two cases of chorionic epithelioma.

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Clinical Studies

The Cytotoxic Action of Carcinolytic Agents in Tissue Culture*

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DELINEATION of the specific amino acid, salt and vitamin requirements of a mouse fibroblast and of a human carcinoma cell[1–6] permitted the propagation of these cells in a medium containing only demonstrably essential growth factors, in which the omission of a single amino acid or vitamin, of glucose or serum protein resulted in cessation of growth and cell death. Additional normal and malignant human and animal cells have been cultured directly from the animal host into media embodying these same minimal requirements but supplemented with 10 to 20 per cent whole serum,[7–9] and a number of previously established cell lines have been similarly propagated.

The ready induction of specific amino acid and vitamin deficiencies in such cultures[1–4] and their reversal by restoration of the missing metabolite suggested that this tissue culture system might facilitate the study of carcinolytic agents. The many previous approaches to this problem have been recently reviewed.[10] Most of these studies relate to the effects of various agents on tissue explants grown in roller tube cultures, either in a plasma clot or in media embodying high concentrations of serum and tissue extracts; and the effect of the compounds was measured in terms of cell morphology or by the area of cell migration and growth around the tissue explant. The possible advantages of a test system in which (1) the cells were grown as a monocellular layer directly on a glass surface, (2) the cells were in immediate and intimate contact with a relatively defined growth medium and (3) the amount of actual growth as affected by the agent could be determined quantitatively by a simple chemical method[11] appeared to justify reexamination of the problem.

The present article describes the cytotoxic action against a variety of normal and malignant cell lines of fifteen compounds on which there were extensive data with respect to carcinolytic action in experimental animals, whole animal toxicity and antibacterial action.

TABLE I
CELL LINES USED IN PRESENT STUDY

Tissue of Origin	Code Letter and Source
Human carcinoma of cervix	HeLa (Gey)
Human epidermoid carcinoma of nasopharynx	KB (Eagle)
Human intestinal epithelium (embryonic)	G (Henle)
Human liver	T (Chang)
Mouse adenocarcinoma ("sarcoma")	S-180 (Foley)
Human conjunctiva	C (Chang)
Human monocytic leukemia (buffy coat)	J (Osgood J-111)

METHODS

The seven cell lines included in the present study are listed in Table I, and the fifteen compounds are shown in Table II.

* From the section on Experimental Therapeutics, Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda 14, Maryland; and the Laboratories of Microbiology, The Children's Cancer Research Foundation, and the Department of Pathology, Harvard Medical School, at The Children's Medical Center, Boston, Massachusetts. Supported in part by research grants C-2782 and C-937 to The Children's Cancer Research Foundation from the National Cancer Institute of the National Institutes of Health, United States Public Health Service. Presented in part before the 47th Annual Meeting of the American Association for Cancer Research, Inc., April 13, 1956, at Atlantic City, New Jersey.

TABLE II

COMPOUNDS STUDIED FOR CYTOTOXICITY IN TISSUE CULTURE

Compound No.	Trivial Name	Lot Number	Source of Sample*	Chemical Name
1	Aminopterin	7-7491	1	4-Aminopteroylglutamic acid
2	Amethopterin	7-8528	1	4-Amino-N^{10}-methylpteroylglutamic acid
3	Bremfol	7-8942	1	Pteroyl-9-methylglutamic acid
4	Amino alanfol	7-8514	1	4-Aminopteroyl-DL-α-alanine
5	An-fol-A	7-7469A	1	Pteroylaspartic acid
6	Amino anfol	7-8686	1	4-Aminopteroylaspartic acid
7	Azaserine	236X34-6V	2	O-Diazoacetyl-L-serine
8	Stylomycin	7-8340	1	6-Dimethylamino-9-(3′-f-methoxy-L-phenylalanylamino-3′-deoxy-D-ribosyl)-purine
9	6-MP	AN32187	3	6-Mercaptopurine
10	JF-5	1687-C-41A	1	Actinomycin D
11	TEM	7-5440	1	N′,N′,N″-Triethylenemelamine
12	Thio-TEPA	7-8940	1	N′,N′,N″-Triethylenethiophosphoramide
13	Daraprim	50-63	3	2,4-Diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine
14	D-54·HCl	PL 161 I/C	4	4,6-Diamino-1-(3′,4′-dichlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine
15	D-69·HCl	HK 31 B/B	4	4,6-Diamino-l-(*m*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine

* 1, Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.
2, Parke, Davis & Co., Detroit, Michigan.
3, Burroughs Wellcome Laboratories, Tuckahoe, N. Y.
4, Children's Cancer Research Foundation, Boston, Mass.

Stock cultures of the various cell lines were grown as an adherent layer in 1 L. Blake bottles in the basal medium previously described.[1–6] This medium embodied the thirteen essential amino acids, seven essential vitamins, salts and glucose, each in a concentration optimal for the growth of the HeLa cells, and was supplemented with 10 per cent human serum in the case of the human cell lines and 5 to 10 per cent horse serum in the case of the two mouse cell lines. When the cultures in the bottles were fully grown, the 15 to 40 million-cell harvest was collected by scraping with a rubber policeman, emulsified with a pipet, counted and inoculated into flat T-15 flasks[1,12] in a volume of 2 to 3 ml. per flask containing approximately 200,000 cells. In one of the two cooperating laboratories some of the cell lines, KB and T, (Table I) were harvested by trypsinization. Commercial trypsin (difco 1:250) was added to fresh growth medium to a final concentration of 0.125 per cent. When this was layered over the cells they came off the glass in one to three minutes at 37°C. After gentle emulsification and centrifugation at 200 to 500 r.p.m., the cells were resuspended in fresh medium, counted and the necessary dilution planted at approximately 200,000 cells per flask.

Varying amounts of the compound under test were added to 100 ml. portions of the same basal-serum medium, the final concentration varying in half-log steps from 10 mM down to 0.000001 mM. Twenty-four hours after the cells had been planted, three flasks were washed and the protein content of the adherent cells determined[11] as a zero-time base line. Two or three flasks of each cell line were fed with each of the feeding solutions containing varying concentrations of the compound under study. The same fluid was replaced after two, four, five and six days at 37°C. and the experiment was terminated on the fifth to eighth day at which time the flasks were washed and their protein contents determined.[11]

The microbiologic activity of these compounds (Table VII) was assayed in Streptococcus fecalis– and Lactobacillus casei–PGA bioassay systems.[13] Each compound was titrated in the presence of the minimal concentration of PGA supporting maximal growth in each test system, and optical density at 650 mμ was read after twenty-four or forty-eight hours incubation at 37°C. Appropriate medium and metabolite controls were included with each assay. The 50 per cent minimal inhibiting dose[14] was interpolated from these data and the antifolic activity was expressed relative to that of crude "X-methyl-PGA" in the same systems.[15–17]

EXPERIMENTAL DATA

The microscopic appearance of a test series (S-180 vs. D-54 dihydrotriazine) forty-eight and ninety-six hours after the addition of the compound is illustrated in Figure 1. An experiment with amethopterin tested against three different

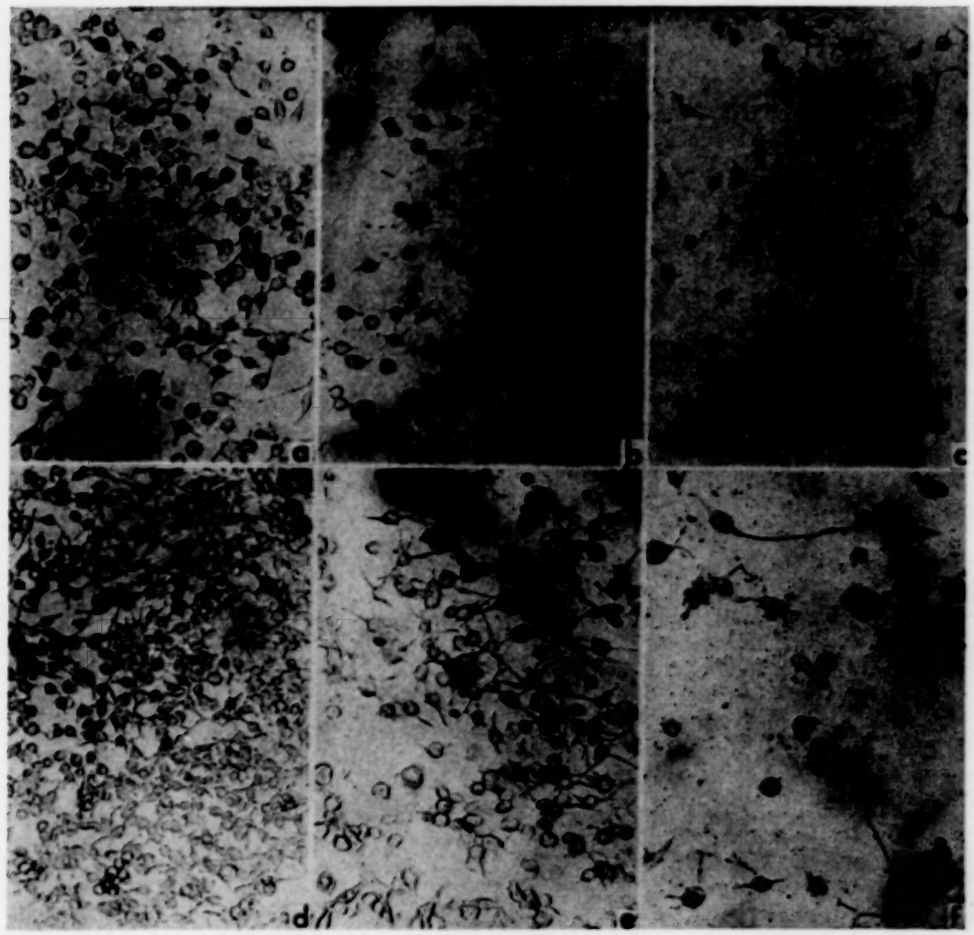


FIG. 1. The progressive cytotoxic effect of a dihydrotriazine (D-54.HCl) on S-180 in tissue culture. Forty-eight hours: (a) control, normal growth; (b) D-54 at 3×10^{-5} mM; (c) D-54 at 3×10^{-6} mM. Ninety-six hours: (d) control, normal growth; (e) D-54 at 3×10^{-5} mM; (f) D-54 at 3×10^{-6} mM.

cell lines in each of two laboratories is summarized in Table III. The consistent results obtained with cell lines which varied widely with respect to the tissue of origin are particularly to be noted, and are further evidenced in Figure 2, in which similar experiments with four different compounds are summarized. (For purposes of clarity the figure shows the results with three cell lines only.) The wide differences in the cytotoxicity of the compounds, ranging from absence of an effect at 1 mM in the case of bremfol to 90 per cent inhibition of growth with aminopterin at 0.00001 mM, are evident in this figure as is the essentially uniform susceptibility of all the cell lines to a given agent.

The ID_{50}* of each compound against each cell line is given in Table IV; the last column in that table lists the relative cytotoxic activity of the compounds, expressed as the average reciprocal of these ID_{50} levels. The data of Table IV are shown graphically in Figure 3 in which the various cell lines are identified by code letters. As shown there, Sarcoma 180 had an anomalous susceptibility to amino anfol, azaserine and the D-69 dihydrotriazine. (Fig. 3.) In general, however, the striking aspect of the results was the essentially uniform susceptibility of the seven lines tested.

* Concentration which caused a 50 per cent inhibition of growth. (Fig. 2 and Table III.)

COMMENTS

Correlations between Cytotoxicity, Carcinolytic Action, Whole Animal Toxicity and Antibacterial Action. The compounds studied included thirteen with definite carcinolytic activity, either in animals or

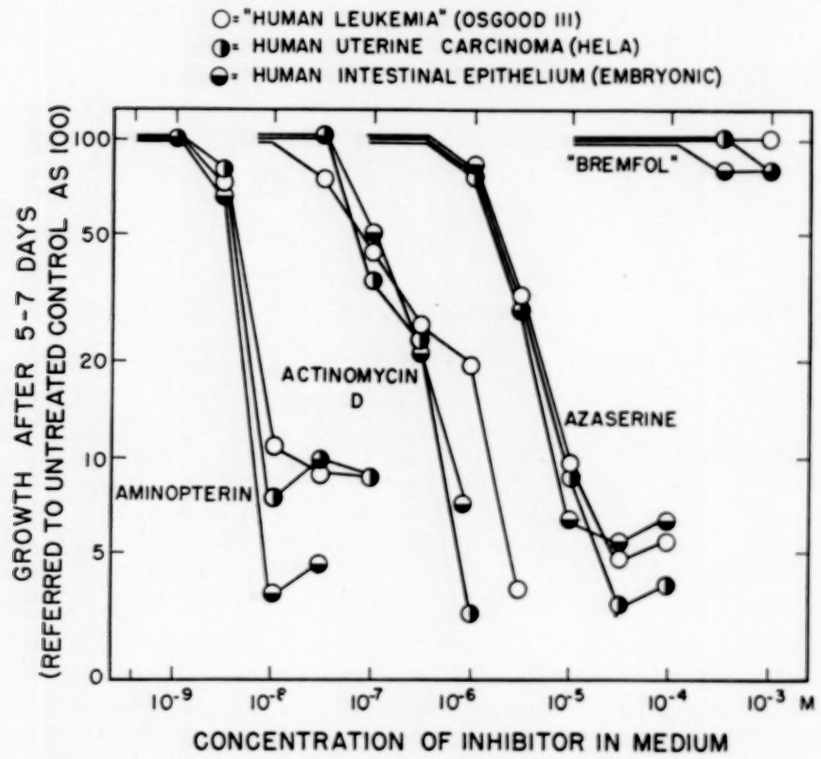


FIG. 2. The cytotoxic effect of four representative compounds on three human cell lines in tissue culture.

TABLE III

THE CYTOTOXICITY OF AMETHOPTERIN AGAINST SIX NORMAL AND MALIGNANT CELL LINES IN TISSUE CULTURE

Cell Strain*	Inoculum		Time in Days	Concentration of Amethopterin in Test Medium,§ mM					ID_{50}‖ mM
	No.†	Protein,‡ γ		0	3×10^{-6}	10^{-5}	3×10^{-5}	10^{-4}	
				Cell Protein in Culture after 6 to 7 Days					
Human carcinoma (HeLa)	2×10^5	184	6	2,577	2,495	2,679	466	171	0.000019
Human carcinoma (KB)	2×10^5	290	7	1,090	1,240	712	478	275	0.000026
Human leukemia (J-111)	2×10^5	163	6	2,117	2,175	2,077	465	228	0.000019
Human embryonic intestine (G)	2×10^5	150	6	2,350	2,470	2,300	332	102	0.000020
Human liver (T)	2×10^5	112	7	1,140	1,065	940	565	...	0.00003
Mouse sarcoma (S-180)	2×10^5	135	7	1,340	1,280	850	335	171	0.000015

* See Table I.

† Approximate number of cells inoculated.

‡ Average protein content of 2 or 3 flasks at time of first feeding (24 hrs. after planting) measured with Folin-Ciocalteu reagent and expressed in terms of its crystalline bovine albumin equivalent.[11]

§ Basal medium embodying 13 essential amino acids, 7 essential vitamins, salts and glucose supplemented with 5 per cent horse serum for S-180, and 10 per cent human serum for the other 6 strains.

‖ By interpolation on semi-log plot.

TABLE IV

THE ID_{50}* CONCENTRATIONS OF FIFTEEN COMPOUNDS AGAINST SEVEN CELL LINES IN TISSUE CULTURE

Compound	ID_{50} Concentration (mM) of Indicated Compound vs.							Average "Cytotoxic Activity"†
	Human Carcinoma (HeLa)	Human Carcinoma (KB)	Human Leukemia (J-111)	Human Conjunctiva (C)	Human Intestinal Epithelium (G)	Mouse Sarcoma (S-180)	Human Liver (T)	
1	.0000045 .0000028	.0000064	.0000061 .0000048	.0000024	.0000048 .0000043	.0000058	.....	220,000
10	.0000056	.0000125	.0000064	.0000054	.0000042	.0000064	.....	165,000
2	.000019	*.000026*	.000019	.....	.00003	*.000019* *.000015*	*.00003*	47,000
14	.00018	.00027	.00019	.00025	.00016	.000048	.....	6,200
8	.00011	*.00019*	.00022	.....	.00014	.0007	*.00049* *.00026*	4,200
6	.00022	.00039 .00024	.0006	.00054 .00042	.00057	.000056	.....	3,400
15	.00033	*.00037*	.00037	.....	.00046	*.0007*	*.00017* *.00018*	2,700
11	.001	.0016	.0008 ±	.0017	.0006 ±	.0021	.....	840
7	.0019	.0018	.0022	.0014	.0021	*.00027*	.....	740
4	.0024	*.003*	.0018	.....	.001	.0021	.0026	490
9	.0024	*.0031* *.0029*	.0019	.....	.0022	*.0013*	*.002*	480
12	.012 .0064	.0096	.0094 .0068	.0068	.0078 .005	.009	.....	130
13	.01	*.03* *.024*	.007	.....	.005	.0048	*.009* *.0056*	120
5	>0.1	>0.1	>0.1	.....	>0.1	>0.1	>0.1	<10
3	>1	>1	>1	>1	>1	>1	>1	<1

* Millimolar concentration which inhibited growth 50 per cent (see Table III.) Each number in the body of the table represents an individual experiment, similar to those of Table III. The italicized figures represent the results of experiments performed in laboratory A, the others in laboratory B.

† Mean reciprocals of the ID_{50} levels for the six cell lines tested with each compound; because of occasional skew values with the S-180 culture, geometric means were calculated throughout.

man, and two folic acid analogues essentially devoid of such activity *in vivo*.[18–19] The two inactive compounds had no effect in tissue culture at the highest concentrations used in this study, while all thirteen "positive" agents were highly cytotoxic. This qualitative correlation is the most significant aspect of the present experiments. The cytotoxic activity, expressed in terms of the concentration which sufficed to produce a 50 per cent inhibition of growth (ID_{50}), varied 2000-fold, from aminopterin with an ID_{50} of 0.0000024 to 0.0000064 mM, to thio-TEPA which was similarly effective at concentrations of 0.005 to 0.012 mM.

Cytotoxicity in tissue culture vs. carcinolytic action in vivo: Table V lists most of the available data with

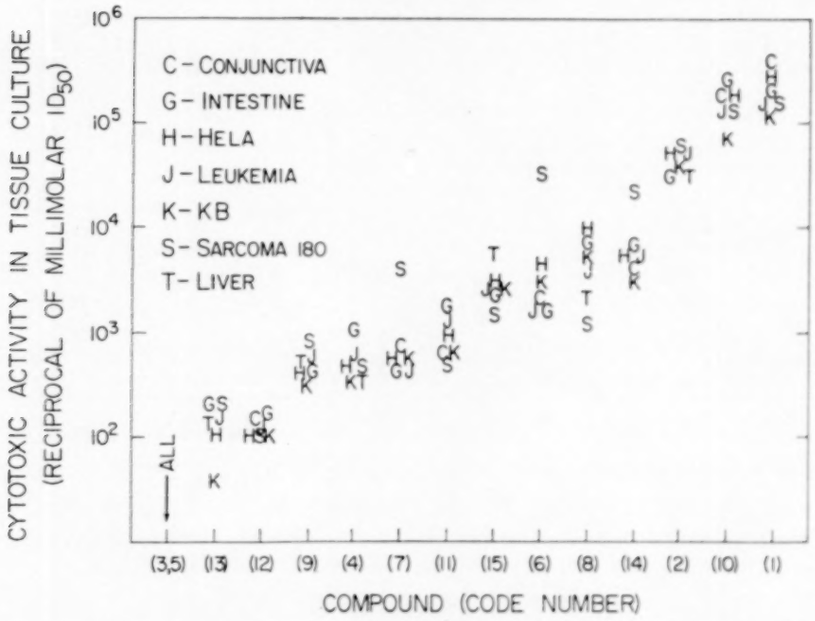


FIG. 3. The essentially uniform susceptibility of seven normal and malignant cell lines to a number of carcinolytic agents.

respect to the efficacy of these compounds on experimental tumors *in vivo*. The compounds have been separated into two groups: the six folic acid analogues in one and the nine miscellaneous compounds in the other. In Figure 4 the antitumor activities of the folic acid analogues have been plotted against their relative cytotoxic action *in vitro*. The high degree of correlation is clear from that figure and from Table v. With the other nine compounds, however, there was no such quantitative correlation. In several instances the discrepancies reflected differences in the therapeutic response of different tumors to a given agent, rather than a qualitative disparity between the results in tissue culture and in animals. Thus compound D-69 (No. 15) was inactive against the S-180 tumor *in vivo*, but its effect against several mouse leukemias was consistent with its average cytotoxicity *in vitro*. Again, 6-mercaptopurine (No. 9) was inactive against a mouse lymphosarcoma *in vivo* but was "normally" active against S-180, L-1210 and a miscellany of other solid tumors. Stylomycin (No. 8) had minimal activity against S-180 and was inactive against the other tumors listed in Table v, despite its significant cytotoxicity *in vitro;* but it has been found to have definite carcinolytic activity against an experimental mammary adenocarcinoma.[22] Azaserine (No. 7) and thio-TEPA (No. 12) were, however, considerably more active *in vivo* than would have been anticipated from their cytotoxic action *in vitro*.

Cytotoxicity in tissue culture vs. whole animal toxicity: The correlation between cytotoxicity in tissue culture and acute whole animal toxicity is shown in Table vi. The overall coefficient of correlation for the fifteen compounds under study, based on relative ranks, was 0.50. If the six folic acid analogues were considered separately (Table vi and Figure 5), there was a high degree of correlation (0.75) with only an-fol-A® (No. 5) showing an abnormally high toxicity *in vivo*. For the remaining nine compounds, however, there was no significant correlation (0.05) between animal toxicity and cytotoxicity.* The contrast in this respect between the antifolic agents and the other nine compounds is evident in Figure 5.

Cytotoxicity in tissue culture vs. antibacterial action: Twelve of the fifteen compounds studied were tested with respect to their antibacterial action against Str. fecalis and Lact. casei. The results of these previously reported antifolic assays are listed in Table vii in terms of their inhibitory activity relative to that of a reference compound (crude X-methyl folic acid). Since the antibacterial systems used in these assays were devised

* With these nine compounds, again unlike the antifolic agents, there was no regular correlation between whole animal toxicity and carcinolytic action *in vivo*.

TABLE V

CORRELATION BETWEEN CYTOTOXIC ACTIVITY IN TISSUE CULTURE AND ANTITUMOR ACTIVITY IN VIVO

Code No. of Compound (see Table II)	Range of ID_{50} (mM) against 6 Different Cell Lines in Tissue Culture	"Effective Dose" against Various Tumors *in vivo*							
		Sarcoma 180		Mouse Leukemia*		Mouse Lymphosarcoma		Other	
		mg./kg.	Reference	mg./kg.	Reference	mg./kg.	Reference	mg./kg.	Reference
Folic acid analogues:									
1	.0000024–.0000064	0.2	18–20	0.225–0.5	18	.....	..	.....	.....
2	.000015–.00003	1.5–2.0	18–21	3.0	18,27,33	1.5–2.0	28	0.75–8.0	27,28,30, 32
6	.000056 –.0006	45.0–50.0	18–20	25.0	18	.....	..	.....	.....
4	.001 –.003	Negative	18,19	25.0	18	.....	..	.....	.....
5	>0.1	Negative	18–20	150.0	18,19	.....	..	.....	.....
3	>1.0	Negative	18–19	Negative	18,19	.....	..	.....	.....
Other compounds:									
10	.0000054–.0000125	0.075	18	0.075	18	.....	..	0.075	18
14	.000048 –.00027	200.0	18	25.0	18	.....	..	.....	.....
8	.00011 –.0007	200.0	18,22	Negative	18,22	.....	..	.....	.....
15	.00018 –.0007	Negative	18	50.0	18	.....	..	.....	.....
11	.0006 –.0021	25.0	18,23–25	25.0	18,26	.....	..	.....	.....
7	.00027 –.0022	5.0	21	2.0 –8.0	18,27,34	5.0	28	3.0–20.0	27,29–32
9	.0013 –.0030	50.0	21	40.0	18,27,34	Negative	28	25.0–50.0	28–32
12	.005 –.012	?		2.5	18	.....	..	.....	.....
13	.0048 –.01	125.0	21	75.0	18,27	Negative	28	Negative	28–32

* L-1210, C-1498 or P-1534

primarily for the detection of antifolic activity, the compounds have again been considered in two groups: the six folic acid analogues, all of which were synthetized with that activity in mind, and the remaining nine compounds. As seen in Table VII, in the antifolic series there was a high degree of correlation between cytotoxic activity in tissue culture and antibacterial action. With the miscellaneous group of compounds, however, there was no significant correlation between cytotoxicity and antibacterial action, presumably indicative of the fact that the cytotoxicity of these compounds was not regularly due to their antifolic activity.

The failure of the antitumor activity of these miscellaneous compounds to relate to their antifolic activity is not surprising. It remains to be seen whether a more generalized antibacterial system can be devised which in a heterogeneous group of compounds would show a satisfactory correlation with either carcinolytic action *in vivo* or cytotoxic activity *in vitro*.

General considerations: In the six folic acid analogues included in the present series there was a highly satisfactory correlation between cytotoxicity in tissue culture, whole animal toxicity, carcinolytic activity and antibacterial action in a test system devised for the detection of antifolic activity. One may reasonably conclude that with these six compounds, all four of these effects are determined by and are quantitatively related to their antifolic activity.

With the remaining nine compounds, however, there was no regular quantitative correlation between cytotoxic action in tissue culture and either carcinolytic action *in vivo*, acute toxicity in mice or antibacterial action in a folic acid test system.

The Equal Susceptibility to Carcinolytic Agents of Normal and Malignant Cells in Tissue Culture. One of the most interesting aspects of the data reported herein is the paradoxic observation that cell lines deriving from normal and malignant tissues were more or less equally susceptible to a

given agent (Fig. 2) despite the fact that with the antifolic agents this cytotoxic effect quantitatively paralleled carcinolytic action *in vivo*. (Fig. 4 and Table v.) The question therefore arises as to the basis for the selective action of these agents on tumors *in vivo*. One possibility is

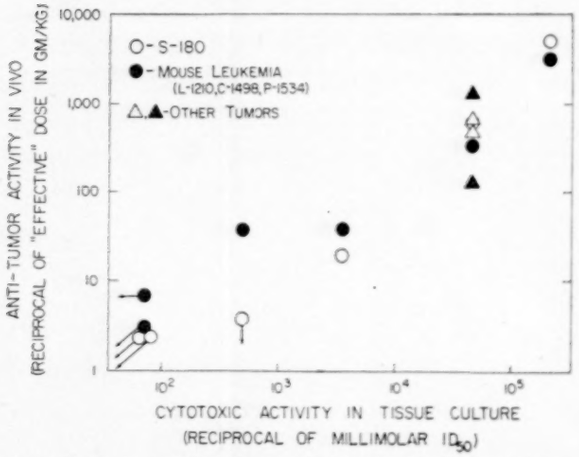


FIG. 4. The correlation between the carcinolytic activity *in vivo* and cytotoxic activity *in vitro* of six folic acid analogues.

that although the cell lines here studied derived originally from normal and malignant tissues, after prolonged cultivation *in vitro* all the strains may have been modified toward a common cell type with similar biochemical and biologic properties. On this thesis it would become necessary to conclude that all the cells had been modified to assume at least some of the characteristics of malignant cells, for their susceptibility to one group of cytotoxic agents *in vitro* did parallel their therapeutic action in experimental tumors.

A second possibility is that normal and malignant cells may be equally vulnerable to these agents under conditions of *in vitro* cultivation, when the cells are growing at comparable rates in an identical environment. In the host, however, their metabolism may be differentially modified either qualitatively, quantitatively or both; and such selective action as these compounds possess *in vivo* may reflect these host-imposed differences in metabolic activity.*

The Possible Screening of Carcinolytic Agents in Tissue Culture. It is apparent that the tissue culture system used in these experiments provides a direct experimental approach to the mode of action of those agents known to have carcinolytic action *in vivo*. Perhaps of greater immediate importance, however, is the possibility that the tissue culture technic may serve as a simple screening method for the detection of carcinolytic agents.* Technically, the procedure is simpler, more reproducible and more easily quantitated than is the evaluation of these agents against

TABLE VI
COMPARISON OF ACUTE WHOLE ANIMAL TOXICITY (LD_{50}) WITH CYTOTOXIC ACTIVITY IN TISSUE CULTURE

Code No. of Compound (see Table II)	Range of ID_{50} (mM)* against 6 Different Cell Lines in Tissue Culture	Acute Toxicity in Mice: LD_{50} mg./kg.	Reference
Analogues of PGA:			
1	.0000024–.0000064	3.6	35
2	.000015 –.00003	89.0	35
6	.000056 –.0006	225.0	35
4	.001 –.003	1000+	36†
5	>0.1	220.0	36
3	>1.0	1000+	36
Other compounds:			
10	.0000054–.0000125	0.67–0.74	38
14	.000048 –.00027	520.0	39
8	.00011 –.0007	422.0	36
15	.00018 –.0007	220.0	36
11	.0006 –.0021	2.8	40
7	.00027 –.0022	254.0	36
9	.0013 –.0030	227.0	41
12	.005 –.012	606.0	36
13	.0048 –.01	92.0‡	37

* See Table IV.
† Mouse toxicity data obtained with same lot of compound used for cytotoxic studies in tissue culture.
‡ Oral dose; all other injected intraperitoneally.

* The bactericidal action of penicillin may be cited as a case in point. *In vitro* under conditions of rapid growth penicillin is rapidly bactericidal, for example, on Streptococcus hemolyticus. *In vivo*, however, it is rapidly bactericidal at a focus of infection only as long as the organisms similarly are in a phase of active growth. When the focus of infection becomes "saturated" with organisms so that the number of bacteria at that focus stabilizes, they then become paradoxically resistant to the bactericidal action of the drug.[47] If the carcinolytic activity of some of these compounds is similarly dependent upon metabolic activity, then a cell growing rapidly *in vivo* could be correspondingly more susceptible.

* One consideration deserves emphasis in this connection. The carcinolytic agents now available have only limited usefulness in man, those limits imposed in large part by their toxicity. Whether the hoped for selective agents which act primarily on the tumor cell will be uncovered by the "rational" screening of compounds designed to have a specific metabolic effect, by "arational" random screening, or whether a more satisfactory treatment of cancer will evolve from basic studies on, for example, the nutrition and metabolism of normal and tumor tissue, is conjectural. However, if compounds are to be screened for carcinolytic activity, the use of normal and malignant human cells in tissue culture as a test object may provide a useful adjunct technic.

animal tumors; and if it could be used as a primary screen, reserving the more cumbersome and more costly animal technic for those compounds found to be effective *in vitro*, a large scale screening survey would be materially facilitated. Two questions must, however, be answered in a

TABLE VII

COMPARISON OF CYTOTOXIC ACTIVITY IN TISSUE CULTURE WITH INHIBITORY ACTIVITY IN BACTERIAL FOLIC ACID-BIOASSAY SYSTEMS

Code No. of Compound (see Table II)	Mean Cytotoxic Activity in Tissue Culture*	Relative Activity† in PGA Bioassay Systems vs.			
		Streptococcus Fecalis 8043‡	Reference	Lactobacillus Casei 7469‡	Reference
Analogues of PGA:					
1	220,000	76	19,36	4,900	36
2	47,000	152	19,36	10,000	36,46
6	3,400	45	19,36	2,900	36
4	490	0.2	19,36	120	36
5	10	0.6	19,36	390	36
3	1	0.016	19,36	10	36
Other compounds:					
10	165,000	7	42	20	42
14	6,200	4	43	0.5	44
8	4,200	0.00015	36	0.0001	36
15	2,700	2	43	0.9	44
11	840	0.00015	36	0.0005	36
7	740	0.0015	36	0.005	36,46
9	480	0.0015	36	0.005	36,46
12	130	0.00015	36	0.0005	36
13	120	3	36,45	0.5	36,46

* See Table IV.

† Referred to similar activity of X-methyl-folic acid as one[15-17] and based on ID_{50} concentrations.

‡ American Type Culture Collection numbers.

much larger series of compounds than have been studied here: (1) what is the incidence of false negative reactions, that is, how many compounds with definite carcinolytic activity *in vivo* would be missed by a tissue culture screen; and (2) what is the incidence of false positives, that is, how many compounds definitely cytotoxic by some arbitrary standard would be devoid of carcinolytic activity *in vivo*. Of these, the former is by far the more important. An *in vitro* technic for the detection of chemotherapeutic agents will necessarily fail to pick up compounds which are in themselves inactive but which are modified *in vivo* to an active form, for example, paludrine,[®48,49] and pentavalent arsenicals, and those which may act only indirectly by virtue of an effect on some locus other than the offending cells, for example, hormones and drugs affecting blood supply. If, however, it should prove that almost every agent which has been uncovered as the result of animal tumor studies would also have been detected by a tissue culture screen, it would appear that these compounds act directly, and serious consideration must then be given to the possible usefulness of tissue culture as a routine screening method.

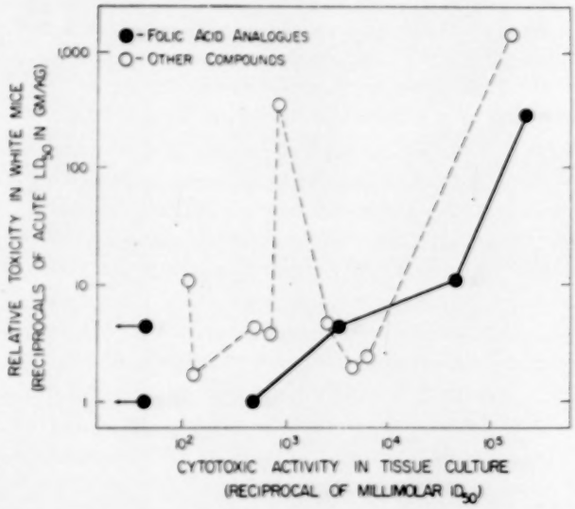


FIG. 5. The correlation between cytotoxic activity and whole animal toxicity in fifteen carcinolytic agents.

If further investigation gives such assurance with respect to the incidence of false negatives, the question of false positives becomes of secondary importance. Thus if one compound in a thousand were actually carcinolytic *in vivo*, and if a tissue culture screen picked up as positive that compound as well as nine others which were cytotoxic in tissue culture but inactive *in vivo*, the tissue culture screen would nevertheless have been effective and worthwhile, for only ten compounds would then have to be tested in animals instead of 1000.

SUMMARY

Thirteen compounds known to have antitumor activity in experimental animals and two compounds essentially devoid of such activity have been studied with respect to their cytotoxicity in tissue culture against three cell lines deriving from normal human tissue, three lines deriving from malignant human tissue and one culture deriving from a mouse sarcoma.

1. All thirteen compounds with definite antitumor activity *in vivo* were highly cytotoxic *in vitro*, while the two inactive compounds were similarly inactive in tissue culture. The cytotoxicity of the thirteen active compounds,

expressed as the concentration necessary to cause a 50 per cent inhibition of growth, varied 2000-fold from an average of 0.000005 mM in the case of aminopterin to 0.008 in the case of thio-TEPA; but in general, a given compound was equally active against both normal and malignant cells.

2. In the six folic acid analogues there was a high degree of correlation between cytotoxicity *in vitro*, carcinolytic activity *in vivo*, acute toxicity in mice and antibacterial action in a system designed for the detection of antifolic activity. With the remaining miscellaneous compounds, however, there was no apparent correlation between cytotoxicity in tissue culture and either acute toxicity in mice or antibacterial activity in the specific assay system used, and the correlation between cytotoxicity and carcinolytic activity was qualitative rather than quantitative.

3. The implications of these data, with particular reference to the possible usefulness of tissue culture for the screening of carcinolytic agents are discussed.

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Hypercalcemia in Malignant Disease without Evidence of Bone Destruction*

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SINCE 1950 we have observed ten patients with hypercalcemia in association with malignancy but without evidence of bone destruction. In three of these, removal of the tumor was followed by a prompt fall in the serum calcium; in one, recurrence of the tumor was again associated with hypercalcemia. In seven patients no abnormality was found at autopsy in the parathyroids, bones or kidneys to account for the hypercalcemia. None of these cases presented the usual clinical and pathologic causes associated with hypercalcemia. Thus there was no evidence for hyperparathyroidism[1] at operation in two patients or at autopsy in seven. There had been prolonged immobilization,[2] no vitamin D intoxication,[3,4] and no excessive ingestion of milk and alkali.[5] There was no evidence for multiple myeloma[1] or Boeck's sarcoid.[6]

The association of hypercalcemia with metastatic malignancy, treated or untreated with hormones, is usually ascribed to bone metastases.[7–9] Because our cases suggest the presence of mechanisms for hypercalcemia in addition to those already recognized, and because some of the more severe symptoms of hypercalcemia are displayed, it seems appropriate to report them. In the literature two cases have been described of a somewhat similar nature to those we are reporting. Albright and Reifenstein[1] described a patient with hypernephroma with a large metastasis to the sacrum and ilium. The patient had hypercalcemia, hypophosphatemia, hypercalcuria and a normal serum alkaline phosphatase. The parathyroid glands were normal on exploration. Irradiation of the metastasis caused a slight transient fall in the serum calcium. These authors raised the question of whether or not the tumor produced a parathyroid-hormone-like substance. Another case appeared in the case records of the Massachusetts General Hospital.[10] This was a seventy-four-year-old man with a proved but controlled carcinoma of the prostate. In this patient a high serum calcium, normal or slightly elevated serum phosphorus and an elevated serum alkaline phosphatase developed. X-ray revealed no significant bone lesions. At autopsy there was a small localized carcinoma of the prostate and a huge hemangiosarcoma of the liver. The bones of this patient were normal.

Recently, Connor, Thomas and Howard[11] reported two cases of bronchogenic carcinoma with hypercalcemia. After resection of the tumor the serum calcium fell to normal. They suggest that the hypercalcemia was "due to excessive bone resorption resulting from substances introduced into the circulation by the tumors." This is similar to our cases.

Our cases fall into two groups. Those in whom it was possible to diagnose and remove the neoplasm which was associated with the hypercalcemia, and those in whom the neoplastic process was either unsuspected or inoperable.

CASE REPORTS

Hypercalcemia Associated with Operable Tumors

CASE 1. M. T. (P.H. No. 002475), a forty-eight year old woman, was admitted on June 27, 1950 because of 40 pound weight loss, anorexia and vomiting of four months' duration. On examination the striking findings were the cachexia and a soft, nontender, multilobular mass arising in the left adnexal region and extending halfway up to the umbilicus. She was anemic. The erythrocyte sedimentation rate was 117 mm. in one hour. The urine concentrated to 1.023 and was negative for albumin, sugar and Bence-Jones protein. The urea nitrogen was 16 mg. per cent. The serum calcium ranged between 15.7 and 17.9 mg. per cent, (Fig. 1) with serum phosphorus of 2.1 to 3.1 mg. per cent. The serum albumin was 3.6 gm. per cent and globulin 2.8 gm. per cent. X-ray

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of the chest was normal. Gastrointestinal x-ray study, barium enema and proctoscopy were normal. Skeletal survey showed minimal demineralization with no changes suggestive of hyperparathyroidism or metastatic malignancy. The lamina dura of the teeth was intact. The electrocardiogram was normal except for a Q-T interval of 0.28 at a rate of 110.

It was thought that the patient had hyperparathyroidism and an ovarian neoplasm. Because of the immediate dangers of hypercalcemia it was decided to do an exploration of the neck first. This was done under pentothal,® nitrous oxide, ether and cyclopropane. Shortly after induction and before insertion of the intratracheal tube, her heart stopped. The chest was opened and the heart was found in diastole. It was massaged and spontaneous contractions began. It was thought safe to continue the operation and exploration of the neck proceeded uneventfully. Two parathyroid glands on the left and one on the right were identified and appeared grossly normal. A small 0.5 cm. node was removed in the hope that this might be an adenoma but on section this proved to be a normal lymph node. Because of the previous cardiac arrest the sternum was not split. She made an uneventful recovery from these procedures, but there was no change in her serum calcium which continued to range between 14.1 and 17.9 mg. per cent. It was felt that a reasonable effort had been made to exclude a parathyroid adenoma and that one should proceed against the ovarian neoplasm.

At laparotomy a large multicystic tumor was found arising from the pelvis and extending up to the umbilicus. No gross metastases were noted. A bilateral salpingo–oophorectomy and total hysterectomy were done. All of the right ovary could not be removed from the pelvis. The histopathologic diagnosis was papillary adenocarcinoma of the ovary. Careful search did not reveal parathyroid tissue, teratoma or unusual calcification. Tumor tissue was also found in the left ovary. The uterus showed no evidence of an estrogen effect. Postoperatively the patient did well. Three days postoperatively her serum calcium was 11.2 mg. per cent. Six days postoperatively it was 10.3 mg. per cent and the serum phosphorus was 3.1 mg. per cent. The serum alkaline phosphatase showed a transient rise to 7.1 Bodansky units (B.U.). Twelve days later radiotherapy was initiated to a total tumor dose of 4300 r. The patient gained sixteen pounds and her serum calcium remained at 10.5 mg. per cent with phosphorus of 3.4 mg. per cent. Five months after the operation she lost a few pounds in weight (serum calcium 11.6, phosphorus 2.3 mg. per cent, sedimentation rate 110). Six months after the operation a mass became palpable in the lower right quadrant, and the serum calcium rose to 13.4, then 15.5 mg. per cent, the phosphorus to 3.4 mg per cent, then 4.0 mg. per cent with spinal fluid calcium 5.4 and phosphorus 1.4 mg. per cent. After temporary improvement she began to fail and dependent edema and severe abdominal pain developed. The serum calcium then was 16.1 mg. per cent. At the patient's request, she was transferred to a hospital nearer her home. Skeletal x-ray studies there in July, 1951, failed to reveal bony metastases. She died suddenly one week later. Permission for autopsy could not be obtained.

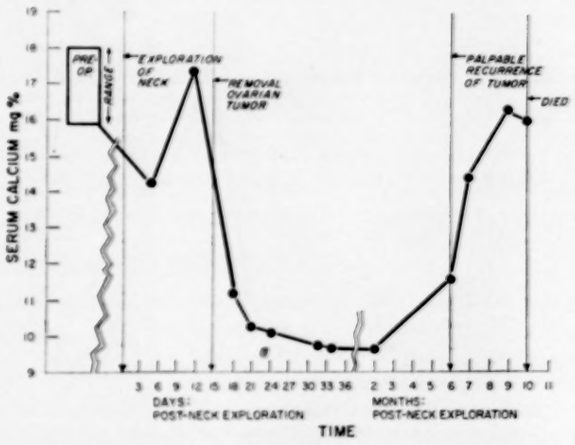


FIG. 1. Hypercalcemia in a patient with ovarian carcinoma.

CASE II. E. L. (P. H. No. 830396), a forty-nine year old man, was admitted on April 1, 1955 with cough and weight loss for nine months and anorexia and nausea for three weeks. His past history was essentially non-contributory. About three years prior to admission he had an episode of painless hematuria, followed by ten minutes of agonizing right upper quadrant pain. The pain subsided and x-rays at another hospital showed no evidence of stones. Although he had no further pain, there were in the following two and one-half years two other brief episodes of painless hematuria. There was no history of vitamin D intake, nor unusual ingestion of milk and alkali.

Physical examination revealed no abnormality other than a non-tender rubbery mass in the right upper quadrant which moved only slightly on respiration. The blood count showed a hemoglobin of 12 gm. per cent. The erythrocyte sedimentation rate was 130 mm. in one hour. The urine concentrated to 1.013; protein and sugar were absent. Microscopic examination showed only 1 to 3 white blood cells. The blood urea nitrogen was 13 mg. per cent. The serum total protein was 6.8 gm. per cent with albumin of 4.2 and globulin 2.6 gm. per cent. The serum calcium ranged between 12.7 to 14.1 mg. per cent, serum phosphorus varied between 2.6 to 3.4 mg. per cent, and the serum alkaline phosphatase 11.4 to 14.1 B.U. The serum acid phosphatase was 2.5 Gutman units. After being on a diet containing only 150 mg. of calcium daily for one week, the twenty-four-hour urinary excretion of calcium was 456 mg. Bone marrow aspiration was normal. X-rays of the chest and skeleton were normal, with no signs of metastases or demineraliza-

TABLE I

HYPERCALCEMIA IN MALIGNANT DISEASE

RESPONSE TO OPERATION

Patient	Sex	Diagnosis	Relation to Operation	Serum Calcium (mg. %)	Serum Phosphorus (mg. %)	Alkaline Phosphatase (Bodansky Units)	Protein Albumin Globulin (gm. %)	Erythrocyte Sedimentation Rate (mm./hr.)	Miscellaneous
M. T.	F	Carcinoma ovary	Preoperative	15.7–17.9	2.1–3.1	3.3	3.6/2.8	117	.....
			3 days postoperative	11.2	.....	.....	.....	.....	.....
			6 days postoperative	10.3	3.1	7.1	.....	.....	.....
			7 mo. postoperative	14.5–16.1	4.5	4.1	.....	120	Spinal fluid calcium 35% of serum level
E. L.	M	Hypernephroma	Preoperative	12.7–14.1	2.6–3.4	11.4–14.1	4.2/2.6	126	Urine calcium
			7 days postoperative	9.2	3.5	7.5	.....	.....	456 mg./24 hrs.
			15 days postoperative	.....	.....	4.5	.....	.....	127 mg./24 hrs.
H. S.	M	Hypernephroma	Preoperative	13.0–14.1	2.5–2.9	14.5	3.6/2.8	110–132	.....
			10 days postoperative	9.1	2.9	7.3	.....	.....	.....
			18 days postoperative	10.3	3.1	5	.....	32	.....

* Metastases present.

tion. X-rays showed intact lamina dura of the teeth. Intravenous pyelograms and aortograms suggested a carcinoma of the lower pole of the right kidney. Throughout this period he had a fever, with daily spikes in temperature to 102°F.

On April 11, 1955 a transabdominal right nephrectomy was performed. There were no demonstrable metastases. Pathologic examination of the kidney showed a clear cell carcinoma of the kidney with tubule formation. There was questionable invasion of the perinephric fat. Seven days postoperatively the serum calcium was 9.2 mg. per cent, serum phosphorus 3.5 mg. per cent, and serum alkaline phosphatase 7.5 B.U. The patient did well until ten days postoperatively when he required a secondary closure of the wound because of a disruption. After this he made an uneventful recovery. Fifteen days postoperatively the serum alkaline phosphatase was 4.5 B.U. and twenty-four-hour urinary calcium excretion had fallen to 127 mg. The patient continued to improve and when seen in the fall of 1955, he had gained thirty pounds and the serum calcium, phosphorus and phosphatase continued normal.

CASE III. H. S. (P. H. No. 245143), a forty-seven-year-old executive, had been in good health all his life. In 1953 embarrassing facetiousness developed, his attention flagged and his memory was poor. Early in 1955 anorexia, postprandial vomiting and weight loss occurred. The only positive finding was an elevated erythrocyte sedimentation rate of 60. In July, 1955 he became somewhat negativistic and apathetic. Studies at another hospital showed a mild anemia, elevated erythrocyte sedimentation rate, serum calcium of 13 mg. per cent serum and phosphorus of 2.3 mg. per cent. X-rays indicated the presence of a right hypernephroma. The patient lapsed into semi-stupor and had to be fed by a nasogastric tube. He was transferred to the Presbyterian Hospital on September 15, 1955, as a case of Alzheimer's disease. On physical examination he had a temperature of 101°, pulse 130, respirations 34 and a blood pressure of 118/76. He was a semi-comatose, cachectic, pale man looking older than his stated age. The general examination was otherwise within normal limits.

On laboratory examination he had a hemoglobin of 10.4 gm. per cent, red blood cell count of 3.4 million and white blood cell count of 8,000 per cu. mm. The erythrocyte sedimentation rate was 110 to 132 mm. in one hour. Urine specific gravity was fixed at 1.012 with 2+ proteinuria, occasional gross hematuria and a mildly positive Sulkowitch reaction. The serum nonprotein nitrogen was 31 mg. per cent. The serum calcium varied between 13.0 and 14.1 mg. per cent, serum phosphorus 2.5 to 2.9 mg. per cent, the serum alkaline phosphatase was 14.5 B.U. The serum proteins showed an albumin of 3.6, and globulin of 2.8 gm. per cent. Paper electrophoretic study was normal. The spinal fluid was normal. X-rays of chest, skull and skeleton were normal. Pneumoencephalogram showed mild diffuse abnormalities. Retrograde pyelograms showed an abnormality of the upper pole of the right kidney.

On October 7, a clear cell carcinoma of the right kidney which had undergone some spindle cell metaplasia, hyalinization and invasion of blood vessels was removed. There seemed to be some invasion of the peritoneum. Postoperatively the patient began to improve immediately. He became alert and oriented and began to feed himself. Ten days postoperatively the serum calcium was 9.1 mg. per cent, phosphorus 2.9 mg. per cent, and alkaline phosphatase 7.3 B.U. On October 25, the serum calcium was still normal at 10.3 mg. per cent, serum phosphorus 3.1 mg. per cent and serum alkaline phosphatase 5 B.U. The erythrocyte sedimentation rate was 32 mm. and he was discharged essentially well six weeks after admission.

Comment. In these patients (Table 1) there was a direct relationship between the presence of carcinoma and hypercalcemia. Removal of the tumor caused a prompt fall in the serum calcium in a matter of days, and the two patients with renal carcinoma also exhibited an abrupt decrease in the level of serum alkaline phosphatase. The serum phosphorus tended to rise after operation. In the patient with the ovarian carcinoma return of the tumor was accompanied by the return of hypercalcemia. In view of the relative frequency of calcification of hypernephromas,[12] it is interesting that in neither of these cases did calcification occur.

Two of the three patients in this group showed emotional symptoms associated with hypercalcemia. The patient with the ovarian carcinoma had a sudden release from lethargy and return of appetite after her second operation, at which the carcinoma was removed. Patient, H. S., whose semi-stupor was regarded as due to presenile psychosis, within a day of his operation experienced striking improvement in mental attitude and became almost normal. It seems likely that his toxic psychosis was due to hypercalcemia. In the older urologic literature the severe lassitude and depression sometimes seen with hypernephroma and rapid clearing within a day or two of operation has been commented upon.[13] The present study suggests that such changes may also have been a manifestation of hypercalcemia.

Hypercalcemia with Inoperable or Unsuspected Tumors and without Significant Bone Destruction

Case IV. J. G. (P. H. No. 970626), a seventy-three year-old Polish man, was first seen in October 1949 with complaints of weakness, urinary frequency and twenty-five-pound weight loss over the past two years. In addition he had also noted aches in the low back, hip and shoulders. Physical examination showed moderate cachexia. No other significant abnormalities were observed. The hemoglobin was 10.9 gm. per cent, with red blood cell count of 3.45 million per cu. mm. and the white blood cell count was 11,400 per cu. mm. The erythrocyte sedimentation rate was 108 mm. in one hour. The urine was normal. The serum acid phosphatase was 2.8 Gutman units, the serum alkaline phosphatase was 3.9 B.U. The serum proteins were 6.5 gm. per cent, with albumin 4.0 and globulin 2.5. The blood urea nitrogen was 23 mg. per cent. Multiple x-ray studies included chest, skeleton and the gastrointestinal tract; all were normal. The intravenous pyelogram was not satisfactory. The bone marrow aspiration was normal. The patient's course was downhill and he required frequent transfusions to maintain his hemoglobin. Cystoscopy revealed a median bar enlargement of the prostate but the ureteral orifices could not be found. Subsequent intravenous pyelography revealed hydronephrosis and hydroureters bilaterally. He became increasingly drowsy and was only semi-responsive. On January 3, 1950 the blood urea nitrogen had risen to 71 mg. per cent, and the serum calcium at this time was 14.8 mg. per cent with serum phosphorus of 2.7 mg. per cent, and serum alkaline phosphatase of 5.0 B.U. With vigorous hydration the blood urea nitrogen gradually fell to 49 mg. per cent. The serum calcium on January 16, 1950 was 13.6 mg. per cent. He became hypernatremic with a serum sodium of 170 mEq./L. and died on January 22, 1950.

Autopsy revealed a large carcinoma of the right kidney which had extended into the liver, the right renal vein and inferior vena cava, and had metastasized to the lungs and the adrenals. Histologically the tumor contained both large clear cells and very anaplastic forms. There was a moderately enlarged benign prostate causing obstruction with hydroureters and bilateral pyelonephritis. The parathyroid glands were normal. The ribs, sternum, vertebra and right hip showed no evidence of metastases and the bony spicules appeared normal.

Case V. B. L. (F. D. H. No. 4087) a sixty-seven-year-old man, was admitted for treatment of progressive anorexia and vomiting and eleven pound weight loss. Eight years before entry the patient had had massive hematuria at which time a left abdominal mass was noted. Exploratory laparotomy disclosed an inoperable "hypernephroma, Grawitz type." The patient's course was uneventful without recurrence of hematuria and without gastrointestinal symptoms. About two weeks before admission to the Delafield Hospital he complained of increasing nausea, anorexia and occasional vomiting.

On physical examination he was emaciated but in no acute distress. In the abdomen there was a stony hard mass which filled the left side of the abdomen. The mass did not move with respiration and the presence of ascites impeded palpation of other organs or masses. Hemoglobin was 6.8 gm., red blood cell count 3.8 million per cu. mm., white blood cell count 14,000 per cu. mm. The urine specific gravity was 1.015. There was proteinuria and the sediment showed 2 to 5 white blood cells. The erythrocyte sedimentation rate was 90 mm. in one hour. The serum non-protein nitrogen was 43 mg. per cent, and the serum calcium was 13.5 mg. per cent, serum phosphorus 3.4 mg. per cent and alkaline phosphatase 17.6 B.U. The serum sodium was 134 mEq./L., serum potassium 4.8 mEq./L. and chloride 103 mEq./L. The x-rays showed clear lung fields; skeletal survey showed no evidence of bony metastases. Intravenous

pyelograms showed no visualization of the left kidney and only a faint shadow on the right. There was a huge soft tissue mass displacing all the intestinal loops to the right. Retrograde pyelograms showed that the left kidney was at the level of the sacroiliac joint.

The patient's course was marked by confusion, disorientation and progressive weakness. In spite of blood transfusions the hemoglobin remained below 8.5 gm. per cent and, despite the administration of ethylene diamine tetra-acetic acid, the serum calcium continued to rise, reaching 18.8 mg. per cent shortly before death.

Autopsy revealed a large hypernephroma of the left kidney. The right kidney was uninvolved by tumor. The tubules of both kidneys showed hydropic changes and there were calculi present in the calyces and ureters. There was no calcification in other organs. The parathyroid glands were normal grossly and microscopically. There were no metastases in the skeleton and the bony trabeculae were everywhere well preserved.

Case vi. F. E. (F. D. H. No. 3455), a sixty-nine-year-old white Russian housewife, was admitted for evaluation of right leg pain, progressive weakness and lethargy of several months' duration. In 1950 she had a panhysterectomy for carcinoma of the endometrium. She was then well until 1953 when she had pain in left lower leg. Pelvic examination was negative. The hemoglobin was 13 gm. per cent. The erythrocyte sedimentation rate was 40 mm. in one hour. X-rays of the skeleton showed extensive degenerative disease of the spine, but no metastases. The leg pain subsided spontaneously but six months later the patient complained of a pain in the sacrum radiating down both legs. Again physical examination and skeletal x-rays were unchanged. The hemoglobin had fallen to 9 gm. per cent and the sedimentation rate had risen to 67 mm. in one hour. A total of 1800 r of radiotherapy was given for the presumed recurrence of the endometrial carcinoma in the lumbar spine. There was subjective relief but in April, 1954 the patient became confused and lethargic, leading to her admission to the Delafield Hospital one month later.

On physical examination she was disoriented and restless. There was a round, smooth 12 mm. nodule in the left lobe of the thyroid, but otherwise examination was within normal limits. The hemoglobin was 7.6 gm. per cent and the erythrocyte sedimentation rate was 114 mm. in one hour. The urine concentrated only to 1.005 and there was a 1+ proteinuria. The serum calcium was 19.6 mg. per cent, serum phosphorus 2.3 mg. per cent, and the serum alkaline phosphatase 6.2 B.U. At a later date when the serum phosphorus was 2 mg. per cent, the serum calcium was 18.6 mg. per cent with a spinal fluid calcium of 8.8 mg. per cent. An ultrafiltrate of serum had a calcium concentration of 10 mg. per cent. The serum non-protein nitrogen was 32 mg. per cent, serum sodium 132 mEq./L., and the CO_2 62 vol. per cent. Bone marrow showed normal hematopoiesis and no tumor cells. X-ray of the chest showed normal heart and clear lungs. A skeletal survey showed no evidence of bone destruction or metastases.

Despite vigorous hydration the serum calcium only fell to 17. The neck was explored for a possible parathyroid adenoma but the palpable nodule was a nontoxic nodular goiter and four normal parathyroid glands were found. The serum calcium continued in the range of 15 to 19 mg. per cent. With intravenous ethylene diamine tetra-acetic acid the serum calcium could be transiently reduced, but despite this she became more lethargic and died. In the week preceding death the serum non-protein nitrogen rose only to 51 mg. per cent.

At autopsy there were no gross or microscopic abnormalities of the parathyroid glands, nor was there mediastinal parathyroid tissue. Attached to the vaginal stump was a tumor mass, 8 by 10 cm., which extended to the right pelvic wall and spread upward to infiltrate the tissues lying between the psoas muscle and the lumbar column, surrounding the lumbosacral plexus. There was no gross evidence for bony involvement by the tumor except for an area of possible direct extension to the iliac bone. Microscopically the tumor was compatible with an endometrial carcinoma. Sections from the vertebral bodies, iliac bone, sternum, ribs and skull were examined. The only bony involvement found was in the iliac bone where there was direct tumor extension without actual invasion of the marrow cavity. This seemed an unlikely cause for hypercalcemia. The vertebrae showed thin bony trabeculae among large marrow spaces without evidence of increased osseous reabsorption. The kidneys showed pyelonephritis and vacuolization and "hyaline droplets" in the epithelium of the tubules. There was only a rare deposit of calcium in the kidneys and there was no metastatic calcification elsewhere.

Case vii. L. S. (F. D. H. No. 4743), a fifty-three year old white woman school teacher, was admitted for evaluation and treatment of polyuria, polydipsia, anorexia and psychic disturbances. In 1943 the patient had a panhysterectomy for endometrial carcinoma. In 1945 there was the onset of nocturia of eight to ten times which was not explained on a urologic or metabolic basis. In 1948 she noted the onset of asthenia which was considered to be on a psychosomatic basis, although the erythrocyte sedimentation rate was 65 mm. in one hour. In 1950 the patient had migratory arthralgias without joint swelling or fever and anemia was first noted. These symptoms continued and in 1953 she began to have a low-grade fever and complained of abdominal pains. The erythrocyte sedimentation rate was 100 mm. in one hour. The serum calcium was 9.6 mg. per cent, phosphorus 3.6 mg. per cent and alkaline phosphatase 4.3 B.U. In July 1954 exploratory laparotomy showed no evidence of recur-

rent endometrial carcinoma or any other abnormality. Since the spleen was somewhat enlarged, splenectomy was performed but on histopathologic examination it appeared normal. There was only transient relief of her symptoms and in January 1955 she was admitted to the Delafield Hospital for evaluation.

The general examination was normal except for the emaciation. During the remaining ten months of her life she was studied with the greatest care. The laboratory studies showed hemoglobin 8 or 9 gm. per cent which remained unchanged despite transfusion of 6 liters of blood over the ten-month period. The erythrocyte sedimentation rate was persistently 100–150 mm. in one hour. Urine specific gravity was fixed at 1.004; also found were proteinuria, 10 to 15 white blood cells and positive cultures for B. proteus and non-hemolytic streptococcus. The serum calcium was 15.1 mg. per cent and it remained elevated; serum phosphorus 3.6 mg. per cent; serum alkaline phosphatase 4.3 to 6.2 B.U., serum non-protein nitrogen 32 mg. per cent (this remained within normal limits until shortly before her death when it rose to 82 mg. per cent). Extensive radiologic studies showed only a double right renal pelvis and ureter on pyelogram, but no evidence of skeletal metastases. The hypercalcemia was extensively studied. On an intake of approximately 200 mg. of calcium a day her urine contained between 230 to 334 mg. of calcium per twenty-four hours. At a time when the serum calcium was 12.2 mg. per cent the spinal fluid calcium was 5.1 mg. per cent. On a calcium tolerance test she excreted 67 per cent of the intake as opposed to a normal person who might retain 70 per cent. Skin and muscle biopsy specimens showed no evidence of sarcoid or mesenchymal disease. The Kveim test was negative. Empirical trial on cortisone did not lead to improvement. Repeated efforts to locate a pelvic carcinoma were unsuccessful. In spite of supportive care, she steadily declined and died ten and a half months after admission.

Autopsy revealed an anaplastic carcinoma in the right retroperitoneal region with compression of the renal pelvis. The tumor was necrotic and severely infected, as was the kidney. The tumor showed some gland formation and was thought to represent a residue of the old uterine tumor. There was no other evidence of tumor. The hypercalcemia was not explained. The parathyroids were normal and the bones showed only osteoporosis without evidence of destruction. There were a few small foci of hydropic degeneration of the renal tubules, but chiefly the kidneys showed acute and chronic pyelonephritis. There were a few deposits of calcium in the pyramids and stones obstructed one pyramid.

Case VIII. E. L. (F. D. H. No. 4675), a fifty year old Negro woman noted painless supraclavicular lymphadenopathy nine weeks prior to admission. Massive edema of the right leg had developed six weeks earlier. Three weeks before admission she had temperatures up to 101°F. and generalized glandular enlargement was noted. A biopsy of the lymph node revealed the characteristic histopathology of Hodgkin's disease. On physical examination the patient was acutely ill with a temperature of 103°F., pulse 128, blood pressure of 135/85 and respirations of 22. There was generalized glandular enlargement. The heart and lungs were normal. There were no palpable abdominal organs or masses. There was pitting edema of the right leg. The hemoglobin was 11.3 gm. per cent, the white blood cell count was normal. The erythrocyte sedimentation rate was 38 mm. in one hour. The urine specific gravity was 1.015 with 1+ proteinuria and rare hyaline cast. The serum calcium was 13.4 mg. per cent with phosphorus 2.8 mg. per cent and alkaline phosphatase 5.3 B.U. The serum non-protein nitrogen was 24 mg. per cent. The serum sodium was 138 mEq./L., potassium 4.5 mEq./L. and chloride 91 mEq./L. The serum total protein was 7.4 gm. per cent with an increase of alpha-2 and beta globulins on paper electrophoresis. X-ray of the chest showed mediastinal lymphadenopathy. The skeletal survey was negative except for minimal hypertrophic osteoarthritis throughout the spine. Bone marrow aspiration showed normal hematopoiesis. During the remaining three months of her life the serum calcium ranged between 12.8 and 23.1 mg. per cent, the serum phosphorus between 1.9 and 3.6 mg. per cent. The serum alkaline phosphatase remained in a normal range of 3 to 5 B.U. The serum non-protein nitrogen remained normal until her final month, when it rose to 49 mg. per cent. The fever and superficial adenopathy were reasonably well controlled by external irradiation, intravenous nitrogen mustard and cortisone. She continued to have considerable nausea and vomiting which were attributed to hypercalcemia and seemed to respond to parenteral rehydration. On a regular ward diet her twenty-four-hour urine calcium values were 260 to 427 mg. When cortisone therapy with doses of 100 mg. a day was commenced her twenty-four-hour excretion was 294 mg., and after three weeks fell to 58 mg. At this time the serum calcium had declined to 12.8 mg. per cent and serum phosphorus to 3.8 mg. per cent and the alkaline phosphatase was 4.5 B.U. There was transient clinical improvement during this period. But during the last three weeks of her life 100 mg. of cortisone daily and hydration to the point of anasarca were not again associated with a lowering of the serum calcium. Three separate injections of 6 gm. each of ethylene diamine tetra-acetic acid doubled the urinary output of calcium but did not reduce the serum calcium. The patient became progressively more lethargic and died five months after the onset of her illness.

Necropsy showed an organizing, partially recanalized left pulmonary vein thrombus. The left lung was partially consolidated, and microscopically these areas showed tumor infiltration, fibrosis and calcific deposits

in the alveoli. The liver and spleen were grossly normal and only a small number of tumor cells were seen to infiltrate the portal spaces and Malpighian corpuscles. The thyroid was normal and four parathyroid glands were found which were normal in all respects. There was generalized enlargement of the lymph glands throughout the body and these confirmed the diagnosis of Hodgkin's disease. Multiple samples and sections were taken from the calvarium, sternum, ribs, vertebral bodies and pelvis; these showed no bony involvement except for the iliac crest where there was a loose fibrous tissue replacing the marrow spaces and encroaching upon and destroying bone spicules. In the fibrous tissue there were a few large hyperchromatic tumor cells characteristic of the Dorothy Reed cell. There was also one small area in the sternum where there was destruction of a bony trabecula by fibrous tissue with one possible Dorothy Reed cell. In general, there was only a small amount of tumor present in bone and only a very small amount of bone destruction seen.

Case IX. F. E. (F. D. H. No. 5017), a seventy-six-year-old white woman with proved bronchogenic carcinoma, was transferred to the Medical Service for treatment of increasing weakness and loss of appetite. Six months earlier a non-productive cough had developed and x-ray examination revealed a shadow at the base of the right lung. Two months later she was admitted to the Delafield Hospital for treatment. Physical findings were compatible with hypertensive cardiovascular disease but were not otherwise abnormal. Her hemoglobin was 11.1 gm. per cent, white blood cell count 6,650 per cu. mm. The erythrocyte sedimentation rate was 24 mm. in one hour. The urine specific gravity ranged between 1.006 to 1.008 with 1+ proteinuria. At bronchoscopy a nodule was seen at the bifurcation of the right lower bronchus and biopsy showed this to be an undifferentiated carcinoma. Skeletal survey showed collapse of several thoracic vertebrae but the x-ray suggested osteoporosis rather than metastases. A serum calcium was not done.

In the absence of definite evidence for metastases, exploratory thoracotomy was performed. A locally inoperable carcinoma was found. With supervoltage radiotherapy equipment she received a tumor dose of 4000 r in twenty-seven days. Shortly thereafter there was an onset of weakness, anorexia, nausea and stupor, and she was transferred to the Medical Service. The serum non-protein nitrogen was 52 mg. per cent. The serum calcium was 16.9 mg. per cent, phosphorus 2.9 mg. per cent, alkaline phosphatase 3.1 B.U. Twenty-four hour urine excretion of calcium on a regular diet varied from 210 to 275 mg. The erythrocyte sedimentation rate was 47 mm. in one hour and rose later. During the remaining two months of her life repeated skeletal x-rays failed to show evidence of metastases. There was no change in the thoracic vertebrae by x-ray. Bone marrow aspirations were consistently negative. Hydration and ethylene diamine tetra-acetic acid were transiently effective in reducing the serum calcium to 13 mg. per cent. The patient's deterioration was progressive, and she finally died with a serum calcium of 14 mg. per cent and a serum non-protein nitrogen of 32 mg. per cent.

At autopsy there was no gross evidence of tumor in the lungs, mediastinum, brain, liver, retroperitoneum or skeleton. There was a structureless hyaline mass in the lungs in the region previously occupied by tumor, but no neoplastic cells could be seen. Although there was osteoporosis of the skeleton, multiple sections failed to reveal any tumor. There was, however, a large neoplasm localized in the spleen which on microscopic study was typical of a reticulum cell sarcoma. Apparently the patient had been essentially "cured" of her bronchogenic carcinoma only to die from inanition and hypercalcemia possibly secondary to a localized and unsuspected reticulum cell sarcoma of the spleen. Grossly, the parathyroids were normal but in one of the glands on microscopic section there was an adenoma so small as to be of questionable significance.

Case X. J. K. (F. D. H. No. 6787), a fifty-nine-year-old white junk dealer, was admitted with a four-month history of painless cough and occasionally blood-streaked sputum. There had been no fever, but he had lost about twenty pounds in weight. Physical examination revealed only dullness and diminished breath sounds over the right upper lobe and hepatomegaly. His hemoglobin was 11.2 gm. per cent, white blood cell count 12,500 per cu. mm., with 13 per cent eosinophils, 57 per cent neutrophils, 24 per cent lymphocytes and 6 per cent monocytes. The platelet count was 636,000 per cu. mm. The erythrocyte sedimentation rate was 65 mm. in one hour. The urine concentrated to 1.028 and was normal except for a 1+ proteinuria. The serum non-protein nitrogen was 28 mg. per cent with a serum calcium of 10.5 mg. per cent, serum phosphorus 4 mg. per cent and alkaline phosphatase of 2.1 B.U. X-rays showed a huge mass occupying the upper two-thirds of the right lung field. On tomography the right upper lobe bronchus was completely obstructed. Angiocardiography showed that there was mediastinal invasion. Skeletal survey was entirely negative. Bronchoscopic biopsy and sputum studies showed a well differentiated squamous cell carcinoma. The mediastinal involvement precluded operative intervention.

Shortly after admission the patient became confused and poorly oriented. He denied pain or headache. The neurologic examination was normal and his behavior was ascribed to an organic psychosis. The serum calcium at this time was found to be 15.7 mg. per cent and rose over the week to 16.9 mg. per cent. The serum phosphorus was 2.9 mg. per cent and the serum alkaline phosphatase was 4.2 B.U. In spite of hydration the patient's condition deteriorated rapidly

TABLE II

HYPERCALCEMIA IN MALIGNANT DISEASE WITHOUT APPARENT BONE METASTASES AT AUTOPSY

Patient	Sex	Diagnosis	Serum Calcium (mg. %)	Serum Phosphorus (mg. %)	Alkaline Phosphatase (Bodansky Units)	Protein Albumin/ Globulin (gm. %)	Erythrocyte Sedimentation Rate (mm./ hr.)	Miscellaneous
J. G.	M	Hypernephroma	13.6–14.8	2.7	3.9–5.0	4.0/2.5	108	.....
B. L.	M	Hypernephroma	13.5–18.8	3.4	17.6	Paper electrophoresis within normal limits	90	.....
E. E.	F	Carcinoma uterus	17–19.5	2.3	6.2	Paper electrophoresis within normal limits	114	Spinal fluid calcium 47% of serum; ultrafilterable calcium 55%
L. S.	F	Carcinoma uterus	13.2–16.4	3.6	4.3–6.2	Paper electrophoresis within normal limits	125	Spinal fluid calcium 42% of serum; urine calcium 260–429 mg./24 hrs.
E. L.	F	Hodgkin's disease	12–23	1.9–3.5	5.3	Total, 7.4 increase alpha and beta globulins	38	Urine calcium 230–340 mg./24 hrs.
F. E.	F	Carcinoma bronchus. Reticulum cell lymphosarcoma of spleen	13–16	2.9	3.1	Normal	47	Urine calcium 210–275 mg./24 hrs.
J. K.	M	Carcinoma bronchus	15.9–16.9	2.9	4.2	Normal	65	.....

and he died one month after admission, five months after the onset of symptoms.

At autopsy a well-differentiated squamous cell carcinoma had replaced the right upper lobe and there were metastases in the middle and lower lobes. There was extension into the mediastinum. No tumor was found in the liver or brain. Multiple sections from sternum, ilia and vertebrae failed to show gross or microscopic evidence of tumor. There was only some generalized thinning of the trabeculae. The kidneys were entirely normal, with none of the histologic changes occasionally seen with hypercalcemia such as hydropic changes of the tubular epithelium, or calcification. All of the small nodules in the parathyroid area which were sectioned and resectioned proved to be lymph nodes or thyroid tissue.

Comment. This group (Table II) presents the same general features as the group in which operation effected a return of the serum calcium to normal levels. There is a high serum calcium, normal or low serum phosphorus, high erythrocyte sedimentation rate and usually a normal serum alkaline phosphatase. Like the other patients with hypercalcemia associated with hypernephroma, B. L. had elevation of his serum alkaline phosphatase level; however, J. G. demonstrates that a high alkaline phosphatase is not constantly associated with the hypercalcemia of hypernephroma.

The spinal fluid calcium was used as an index of the plasma diffusible calcium. In F. E. the spinal fluid calcium was 47 per cent of the serum level, in L. S., 42 per cent. The normal spinal fluid calcium is about 45 per cent of the serum level. It is possible that the severe mental symptoms of F. E. and L. S. were related to this rise in the absolute level of diffusible calcium. M. T., in the first group, did not have any unusual mental symptoms at a time when her spinal fluid calcium was 32 per cent of the serum level.

In none of these cases, except the patient with Hodgkin's disease, was there any evidence of bone metastases, and in this patient there was bone involvement only by scattered Dorothy

Reed cells. Also, none of the patients revealed the histologic picture of osteitis fibrosa generalisata. There was no hyperparathyroidism.

REMARKS

The mechanism for the hypercalcemia in this total group of ten patients with malignant disease is not clear. It appears unlikely that the hypercalcemia was due to bone replacement or destruction because there was inadequate evidence for this during life or at autopsy and because the serum calcium fell so promptly after removal of the primary tumor. It is also unlikely that this hypercalcemia is due to hyperparathyroidism. The parathyroids appeared normal at operation in two cases and normal at autopsy in seven cases. Again the fall in serum calcium after removal of the primary tumor would argue against primary hyperparathyroidism. The elevated serum alkaline phosphatase in three of the four cases of clear cell carcinoma of the kidney raises the possibility that the serum calcium was being carried in an unionized form, and that the ionized form was sufficiently low to have caused secondary hyperparathyroidism with mobilization of bone salt and consequent rise in serum alkaline phosphatase. However, bony changes of hyperparathyroidism were not found at autopsy and the parathyroids appeared normal.

The fall in serum calcium after removal of the primary tumor suggests that some tumors may produce a substance which behaves like an extract of the parathyroid glands, especially in those cases in which there is an elevation of serum alkaline phosphatase. Although, to date, extracts of these tumors have not shown any calcium-mobilizing ability, and although the bones do not show the changes of osteitis fibrosa generalisata, this possibility cannot be ruled out. A second possibility is that these tumors produce a substance like vitamin D. This might cause excessive absorption of calcium from the gastrointestinal tract similar to that postulated in Boeck's sarcoid.[14] Unfortunately, balance studies to evaluate the fecal calcium were never satisfactory. If a vitamin D-like substance were being produced, it could also cause hypercalcemia by a direct action on bones even in the absence of dietary calcium.[15] A third possibility is that these tumors produce an abnormal substance which binds the calcium and transports it in excessive amounts. It is not clear what the binding substance might be. It does not appear to be reflected in the ordinary Howe fractionation of plasma proteins or in electrophoretic patterns. Preliminary studies to isolate a circulating mucopolysaccharide which could bind calcium have failed. A calcium-binding lipid or cephalin has not been found in adequate amounts to explain the abnormalities observed. The possibility of an increased estrogen effect has been considered but there was no evidence for this in the endometrium of the autopsied cases. There is also the possibility that this hypercalcemia resembles the situation in laying hens. Recently Erickson, Clegg and Hein[16] reported in laying hens, a phosphate-rich lipoprotein with very marked calcium binding. Obviously further work is needed and is in progress to elucidate the mechanism for the hypercalcemia.

The tendency for the serum phosphorus to be low is hard to explain, apart from the general decline observed in patients with marked weight loss. It would be compatible with the concept that these tumors were producing a parathyroid-like hormone which was able to cause a phosphate diuresis. Unfortunately, phosphate balance studies were not done. It can only be said at this time that the bones do not show the ordinary effects classically produced by large amounts of a parathyroid hormone.

Another interesting feature of the patients reported is the degree of mental aberration which a number exhibited. While some lassitude and apathy could be anticipated, several of these patients behaved as though they had a toxic psychosis, which was rapidly reversed in all when the calcium could be lowered.

SUMMARY

1. Hypercalcemia with a tendency to hypophosphatemia is reported in ten patients with malignant disease and normal bones.

2. These patients exhibited symptomatology characteristic of hypercalcemic states, including mental confusion.

3. Removal of the primary tumor in three patients was associated with prompt return to normal of the serum values of calcium and phosphorus and the alkaline phosphatase, when elevated.

4. The parathyroid glands were invariably found to be normal at operation or at autopsy.

5. A possible mechanism for the hypercalcemia in this group of patients is discussed.

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Seminar on Diseases of the Pancreas

Carcinoma of the Pancreas

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THE manifestations of malignant tumors of the pancreas and the periampullary region of the head of the pancreas and duodenum are so protean that any physician, specialist or general practitioner, may be faced with the necessity for diagnosis. The usual course of these tumors is so rapid, the late symptoms are so severe, and the treatment in the advanced case is so unsatisfactory that early diagnosis and immediate treatment, frequently even on a presumptive diagnosis, is essential. As Whipple has said, "To observe the patient for weeks until the diagnosis is obvious is to study the patient to death."

Mondiare[210] and Battersby[15] were apparently among the first to describe carcinoma of the pancreas, although articles in the relatively ancient literature[11] by Alberti, Heurniuns and Topies were referred to by Pitt.[258] In the American literature DaCosta[76] first discussed the problems and signs of cancer of the pancreas. He stressed pain as a diagnostic sign. This is especially significant in view of the fairly common concept of painless jaundice as a diagnostic sign of carcinoma of the pancreas. In 1888 Bard and Pic,[11] in two comprehensive articles, gave excellent descriptions of the clinical manifestations of carcinoma of the pancreas and correlated them with anatomic and pathologic studies. Bosanquet and Pitt[27] stated in 1908 that "accurate knowledge of the diseases which affect the pancreas, can scarcely even now be said to exist; such as we possess is almost entirely the product of investigations since 1888." In 1931 Oberling and Guerin[230] brought together in a monograph the knowledge concerning carcinoma of the pancreas available at that time, both from the literature and personal experience.

For practical purposes a discussion of carcinoma of the pancreas must include carcinoma involving those structures traversing and in close proximity to the head of the pancreas. It is virtually impossible to distinguish these lesions by clinical examination and history, and frequently it is difficult at the time of surgery. Indeed in many instances exact diagnosis is difficult for the surgical or postmortem pathologist, who has the entire specimen in hand. Within a very small area tumors can arise in any one of six structures:[72,126] the common bile duct, the duct of Wirsung, the ampulla of Vater, the papilla of Vater, the duodenal mucosa in the immediate vicinity of the papilla and the head of the pancreas. While carcinoma can arise from any of these structures, it very early penetrates the surrounding tissues and by extension involves the adjacent organs sufficiently to obscure the exact point of origin.[180] In one series, in 182 of 222 cases, all epithelial structures of the papilla were involved. Only one could be said definitely to have arisen in the ampulla of Vater, three arose from the terminal duct of Wirsung, seven arose from the terminal bile duct and four arose from the intestinal mucosa covering the papilla.[180] In approximately two of three anatomic specimens the common duct is surrounded in its distal portion by pancreatic tissue and in the other third it lies in a deep groove within the pancreatic tissue on the posterior surface of the pancreas.[138] Carcinomas arising in the duct or in the surrounding tissue very quickly become indistinguishable,[19,43,207] and tumors of the surrounding pancreas very quickly obstruct or invade the duct. The use of the terms carcinoma of the ampulla of Vater or of the papilla of Vater, frequently used interchangeably, depends upon the point of origin of the tumor and the anatomic structure present.[8,80] Approximately 20 to 30 per cent of anatomic sections reveal a true ampulla with a common channel for the bile and pancreatic duct. This may be from 1 mm. to 15 mm. in length.[70,176,235,270] Carcinoma of the duodenum itself is the most frequent small bowel tumor and most frequently involves the second part.[38,48,99]

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Carcinoma of the pancreas and of the region of the papilla or ampulla is not a common disease. It is encountered in about 0.3 to 0.75 per cent of autopsies. (Table I.) Biach[21] noted the condition in twenty-two of 18,069 autopsies, Segre[289] in twenty-seven of 11,472 autopsies, Park[242] in 226 of 53,000 collected autopsies and Bashford[14A] in 1,000 of 84,448 autopsies.

TABLE I
INCIDENCE OF CARCINOMA OF THE PANCREAS AT POSTMORTEM EXAMINATION

	Total Autopsies	Carcinoma of the Pancreas
Biach[21]	18,069	22
Segre[289]	11,472	127
Park[242]	53,000 (collected)	226
Bashford[14A]	84,448 (collected)	1,000
Hick and Mortimer[139]	7,932	50
Brunschwig[43]	5,200	55

The ratio of carcinoma of the pancreas to all types of carcinoma in postmortem series is about 1.76 to 2 per cent.[108,126,165,172] (Table II.) Carcinoma of the stomach occurs about four to five times as frequently as carcinoma of the pancreas.

It has been estimated that in New York State the probability of cancer of the pancreas is about the same as leukemia, approximately 0.473 per cent in men and 0.419 per cent in women, compared with a figure of 2.277 per cent for carcinoma of the stomach in men and 4.974 per cent for carcinoma of the breast in women.[327] In one county in New York State, with a population of 300,000, eleven cases of cancer of the pancreas were found in one year, 1947.[327] In another series of 12,290 hospital admissions for cancer, carcinoma of the pancreas was noted in 1.1 per cent of the total cases of cancer, and cancer of the papilla and bile buct in 0.3 per cent, a total of 1.4 per cent of admissions for carcinoma.[251,265] (Table III.)

Carcinoma in these sites is predominantly a disease of males, with a sex ratio of about 2 to 3:1.[18] (Table IV.) This is of real significance in differential diagnosis since biliary disease, particularly gallstones, is more common in women.[317] The age incidence is similar to that of carcinoma in general. It is a disease of middle or advanced age, the average age being about fifty-five to fifty-eight years.[18,41,65,77,178] Carcinoma of the pancreas proper would seem to occur in a somewhat younger age group than carcinoma of the papilla of Vater.[207] At least ten patients under twenty years of age, bearing a carcinoma of the pancreas, have been reported, the youngest being seven months old.[148,154,167,238,253,296] There has been no real evidence for racial predisposition, although there would appear to be a slightly greater incidence of carcinoma of the pancreas in the Caucasian as compared to the Negro.[19,98,272]

TABLE II
INCIDENCE OF CARCINOMA OF THE PANCREAS IN RELATION TO THE INCIDENCE OF ALL CARCINOMAS

Postmortem	All Carcinomas	Carcinoma of the Pancreas
Eppinger	308	19
Hick, Mortimer[139]	1,000	50
Bigelow, Ford	4.8% cancer deaths in Massachusetts	.....
Biach[21]	2,005	29
Conn. State Tumor Registry[49]	4,661	104
Ewing[109]	1.76 to 2%	.....
Brunschwig[43]	5,200	5%

Of the malignant diseases in this area, carcinoma of the pancreas is more common than carcinoma of the papilla of Vater and common duct by about three to one, and other malignant tumors are still more rare.[109,130,230] Sarcoma, cystadenocarcinoma and malignant nesidioblastoma are the other types which are occasionally seen.

Primary sarcoma of the pancreas is an uncommon lesion occurring in less than 1 per cent of pancreatic malignancies.[130,221,224,244,258,275] It is seen relatively frequently in children and young adults,[43,167,182,193,198] so frequently that a malignant tumor of the pancreas encountered in a child can be expected to be a sarcoma, although carcinomas do occur below age twenty.[167] Sarcoma is found with equal frequency in the head and tail, with frequent involvement of the entire gland.[198,211] Symptoms occur late, and include pain and pressure effects of the tumor mass. It is usually diagnosed by the presence of a mass which is large and bulky by the time of discovery. Infiltration of the surrounding tissue with adherence to surrounding viscera may be present. Regional and distant metastases may not occur until the tumor has reached very large

size. The microscopic types described most frequently are lymphosarcoma, neurogenic sarcoma, angiosarcoma and spindle cell or fibrosarcoma. Only the latter have been considered true primary sarcomas in most instances.[109,130,153,198,232,276] The diagnosis is usually made only at operation or at postmortem. The first reported resections for tumor of the pancreas, by Trendelenburg[314] and others,[38,41,202] were for sarcoma of the pancreas. Treatment is largely palliative, by surgery and/or radiation therapy. Brunschwig[41] stated in 1942 that he knew of no cure of an authenticated case of sarcoma of the pancreas.

TABLE III
INCIDENCE OF CARCINOMA OF THE PANCREAS IN RELATION TO THE NUMBER OF HOSPITAL ADMISSIONS

	Hospital Admissions	Carcinoma of the Pancreas
Futcher[118]	41,949	58
Kiefer[163]	50,494	59
Leven[178]	57,143	32
Puestow[265]	12,290 for cancer	138 to 182
Sloan, Wharton[294]		.06%
Strang, Walton[305]	347,614	284
Broadbent, Kerman[40]	200,000	.05%

Cystadenocarcinoma is not a distinct entity since it is difficult to differentiate from carcinoma arising in a true cyst and cystic degeneration of a solid carcinoma.[179A] They are irregular, lobulated, cystic tumors, which are blue-red in color. On cross-section they are multiloculated with cysts of irregular size and shape and thick cellular walls.[162] Papillary infoldings are common and are typical of malignant change, although some papillary projections may occur in benign cystadenomas. Microscopic section shows cystic structures lined by irregularly shaped tumor cells, with striking papillary infolding of the tumor lining of the cysts and invasion of the fibrous wall by tumor cells. Solid masses of tumor cells may also be seen. The symptoms are those of an increasing tumor mass in the region of the pancreas with pressure on other organs. The development and growth, the tumor perhaps arising from a benign cystadenoma, may be relatively slow; case histories of several years duration not being very uncommon.[162,179A,283] Cystadenocarcinomas have been reported to develop in previously marsupialized benign cystic lesions.[191,200,283,338] Metastases, which occur late, are most commonly to the lymph nodes and liver, and less commonly and later to distant organs.[153,317] Prolonged survival is frequent after removal.[41,162,179A]

Islet cell tumors (nesidioblastoma) are found to be definitely malignant, as shown by the clinical course, in about 10 per cent of cases, and microscopically or locally malignant in another 10 per cent.[142] Like the benign islet cell tumors, malignant tumors of this type are relatively more frequent in the tail and body than in the head and neck.[35,37] Malignant islet cell tumors are not well encapsulated, daughter nodules may appear, and metastases to the liver, to the lymph nodes and to distant organs occur.[37] The questionably malignant lesion shows irregularity of the cells, mitoses and invasion of the capsule just as do the proved malignant adenomas.[98] The metastatic nodules in truly malignant islet cell tumors are often more cellular than the primary neoplasm, with little tendency toward normal islet cell patterns. Hypoglycemia due to hyperinsulinism and all its bizarre manifestations occurs with malignant as well as benign islet cell tumors.[47] Even if the primary tumor is removed, the metastasis may continue to secrete insulin and maintain the hypoglycemic state.[16]

TABLE IV
SEX INCIDENCE IN CARCINOMA OF THE PANCREAS

	Male	Female
DaCosta[76]	24	13
Ancelet[4]	102	59
Futcher[118]	22	19
Kiefer[163]	18	15
Duff[98]	38	12
Miller et al.[208]	41	16
Grauer[126]	25	9
Rives et al.[272]	78	18
Brown et al.[41]	72	28
Arkin, Weisberg[6]	37	11 (75 cases)
Conn. State Tumor Registry[49]	1.6	1

PATHOLOGY OF CARCINOMA

Of the carcinomas found in the pancreas and its immediately associated structures, those arising in the gland itself are by far the most frequent, about 90 per cent in postmortem series[163,204,207] and 70 per cent in operative series.[55] When carcinoma arises within the gland

substance itself, the head is involved primarily in over 60 per cent, even in postmortem series.[41,77,163,172,178] (Table v.) Extension to involve the entire gland was more common in older series.[4,21,209] (Table v.) Rarely, carcinoma may arise in aberrant pancreatic tissue.[10]

TABLE V
SITE OF TUMOR WITHIN THE PANCREAS

	Head	Body	Tail	General	Undetermined
Kiefer[101]	24	3	2	4	..
Lancereaux[170]	11	2	2	..	..
Mirallie[205]	39	3	4	19	..
Oser[208]	20	2	3	1	..
Boldt	25	5	5	18	..
Mikal, Campbell[204]	66	Both 34		..	..
Arkin, Weisberg[6]	37	12	16	..	..
		Both 8			
		Aberrant tissue 2			
Leven[178]	60	Both 19		18	..
Duff[53]	28	Both 19		3	..
Brown et al.[41]	61	8	15	8	..
		Both 8			
Ancelet[4]	33	5	2	88	72
Biach[31]	19	13	..	31	10
Leach[173]	21	9	2	7	..

Carcinoma originating in the common duct, ampulla or on the papilla may cause obstruction when quite small. Carcinomas have been reported as small as a lymph node[51] or even a cherry pit.[180] At the early stage they are usually distinct, well-demarcated, hard white tumors, although papillary types have been described.[109] Microscopically they have a well differentiated structure. With increase in size they infiltrate the surrounding structures, pancreas and duodenum, lose their distinct character, and are difficult to differentiate from tumors arising in those structures.[72,180,208] Lesions of the papilla and periampullary area ulcerate early and spread as an eroding lesion into the duodenum, with raised, thickened, overhanging, irregular edges.[72] It is these lesions which cause occult blood in the stools and an occasional hemorrhage.[69]

Carcinoma of the pancreas itself is rarely seen as a small tumor except as an incidental postmortem finding or occasionally when it lies in close proximity to and invades or obstructs the common duct causing jaundice. The size of the tumor in reported series varies from 1.5 cm. diameter to 16 by 9 by 9 cm.[19,41,126,130,172,208] Commonly these tumors are dense, scirrhous, lobulated or coarsely nodular tumors with indistinct margins due to infiltration.[109,163,172,187,208] They frequently show retraction of the overlying gland.[19,163] Occasionally a rounded bulging tumor is seen, but this is more likely with the less common medullary type or cystadenocarcinoma.[162,187] The centrally placed tumors, if small, may not be apparent or may be felt as a small nodule.

With obstruction of the ducts, chronic pancreatitis occurs distal to the block, with dilatation of the ducts, destruction of the acini and replacement with fibrous tissue,[126,135,208] but with preservation of the islets of Langerhans.[135]

Extension of the tumor is direct by invasion of the remaining gland or duodenum, and by adherence of adjacent structures followed by invasion.[19] The adjacent organs most frequently involved are the duodenum, occasionally the stomach, and rarely the colon or kidney.[19] Ulceration into each may occur. The adjacent vessels are frequently involved. Extension may also be by infiltration through the common bile duct or pancreatic ducts or their lymphatic channels or by free cells. This extension is of particular importance in surgical treatment since excision of the ducts and surrounding lymphatics may be inadequate, local recurrence occurring in an otherwise cured case.[65] Extension by the perineural lymphatics[90,207] and those accompanying the pancreatoduodenal vessels is the rule with true pancreatic carcinoma.[207] Inoperability in early cases is frequently on the basis of this perivascular infiltration, especially about the portal vein.[60,62] This type of spread is much less common with ampullary or papilla tumors.[207] Metastases are most frequent to the regional lymph nodes and to the liver. The metastases to the liver may be small but numerous.[154] Other metastases, in their order of frequency, are to lungs, intestines, adrenals, bone, diaphragm, kidney, heart, mediastinum, bladder, ovary, brain, and muscle, skin or subcutaneous tissue.[41,56,101,130,172,178,258]

Microscopically, tumors of duct and acinar origin can be distinguished.[19,163] In general, the duct cell carcinomas are the more scirrhous type containing much dense fibrous stroma with irregular duct-like or glandular structures lined by one or more layers of cuboidal or columnar cells. Medullary carcinoma grows in sheets and banks of cells in a haphazard manner, but with rather uniform size, shape and staining quality of the cells. In some areas ill-defined acini are seen.[19,109,126,130,172,207,289] Anaplastic carcinoma with irregular masses of variegated cells is less

common.[109,130] Squamous carcinoma occurs rarely but must be considered a primary pancreatic cancer.[6,109]

The etiology is of course unknown. Duct metaplasia following inflammatory involvement is suspect and has been shown to be present along with carcinoma *in situ* in uninvolved ducts in glands bearing carcinoma.[9,105,165] Carcinomas have been seen in many animals, particularly dogs,[41] mice[295] and Syrian hamsters[114A] in which it is surprisingly common.

SYMPTOMATOLOGY

Despite the still too widely held opinion that the most common symptom of carcinoma of the pancreas and the papilla of Vater is painless jaundice, almost all authors from the time of DaCosta[76] have observed that *pain* is most frequently the first symptom of carcinoma of the pancreas.[20,41,77,105,163,178,277] It may be the only symptom, especially in patients with carcinoma of the body and tail.[29,31,57,98,305] Pain is the complaint that brings most patients to the doctor and all too frequently from one doctor to another until the patient shows one of the signs of obvious advanced carcinoma. The pain is not diagnostic in any sense but follows three general types:[19,163] (1) a colicky pain, frequently related to the right upper quadrant of the abdomen, which may be more common with papilla carcinoma and may be due to dilatation of the ducts and gallbladder; (2) a steady, dull, mid-epigastric pain which radiates through to the low back; and (3) a paroxysmal pain which begins near the umbilicus and radiates widely to the back, to the front of the chest and over the abdomen. Perhaps the most distinctive feature of the abdominal pain in cancer is "its persistence, week after week until life's end."[41] Eusterman and Wilbur,[99] who noted pain in 86.5 per cent of their cases, described as characteristic of pancreatic pain the epigastric situation, radiation to the back, the frequent dull aching character, the moderate severity, the constancy, the steady progression, the exacerbation at night, and the non-relationship to normal events of the digestive cycle. However, typical peptic ulcer pain has been reported in from 10 to 12 per cent of patients.[18,77] In four of twenty patients in another series typical ulcer pain occurred but no ulcer was found at postmortem.[6] Pain is frequently present for a long time before definitive treatment is finally achieved, as many as 22 to 29.8 per cent of the patients having had pain as a major complaint for more than five months before admission to the hospital;[55,61] indeed, cases of patients with several years' duration of pain have been reported.[128,163,218] Investigation by electrical stimulation confirmed the pain distribution.[23] Stimulation of the head gave pain in the right upper quadrant; of the body, pain in the mid-epigastrium; of the tail, pain in the left upper quadrant, and of the total pancreas, a band of pain extending through to the back. The cause of pain in carcinoma of the pancreas and ampulla of Vater is not completely understood but it is commonly considered that the colicky type of pain is probably due to obstruction of the ducts with distention of the common bile duct and gallbladder.[231] This is confirmed by the fact that cholecystostomy or cholecystenterostomy has been reported to relieve this type of pain.[299] Dilatation of the pancreatic duct (duct of Wirsung) may also produce pain, especially if pancreatitis is produced. The steady persistence of severe pain radiating through to the back is usually considered to be due to invasion of the nerves by carcinoma.[90,178,207] Perineural lymphatics were found to be invaded by malignant cells in 66.6 per cent of pancreatic carcinoma, and in no cases of papillary and duodenal carcinoma.[207] However, in contradiction to this thesis there was no marked difference in incidence of pain in those who did have perineural invasion.[207]

The next most significant symptom is *jaundice*,[12,18,20,209,221] which occurs in about 65 to 80 per cent of cases at the time of admission to hospital.[18,39,77,116,118,163,189,201,208,209,263,277,299] It is the symptom which causes most patients to seek treatment.

Jaundice is more frequent in carcinoma of the papilla or ampulla of Vater, being described in 90 to 100 per cent of the patients with these conditions as compared to 80 to 81.5 per cent of patients with carcinoma of the head of the pancreas in the same series.[207,277] In another series the incidence was found to be almost identical in the head and ampulla, 88 per cent and 87 per cent, but only 27 per cent of those patients with carcinoma of the body and tail had jaundice.[204] In one group of 400 cases of jaundice, of all etiologies, carcinoma of the pancreas was the cause in 11.75 per cent.[134] In another group of 1,035 collected cases of icterus due to pancreatic lesions, excluding only acute pancreatitis, 73 per cent were caused by carcinoma, only 23 per cent were caused by chronic pancreatitis, and a mere

4 per cent were left for all other causes. The intensity of jaundice in malignant obstruction is greater than in most cases associated with non-malignant disease such as chronic pancreatitis.[115] Jaundice with true carcinoma of the pancreas is almost always persistent and steadily progressive. In many cases it becomes extremely deep, with a bronzing effect.[170] Occasionally with carcinoma of the papilla or ampulla there may be remission of the jaundice, due to ulceration of the tumor or relief of spasm or edema and opening of the biliary tract.[35,77,178,320] This may be very misleading in the differential diagnosis of tumor and stone. In almost all instances of carcinoma of the head of the pancreas pain precedes the jaundice whereas jaundice precedes the pain in the majority of patients with ampullary carcinomas.[207] The serum bilirubin is usually higher in carcinoma of the pancreas, icterus averaging 24.5 mg. per cent, than with papilla lesions, averaging 8.5 mg. per cent.[207] This is compatible with observations on the presence of bile in duodenal drainages. Patients who had carcinoma of the papilla showed absence of bile (complete biliary obstruction) in only about 50 per cent of cases whereas 100 per cent of the patients with pancreatic carcinoma showed complete biliary obstruction.[207]

Icterus is usually produced by obstructive growth into the duct or by compression or invasion of the duct by tumor, but on occasion may be produced by metastatic lymph nodes, in a few instances by metastases in the liver or by portal vein thrombosis or vena cava thrombosis.[19] It has been stated that itching is much more common with jaundice in cases of carcinoma of the pancreas and papilla of Vater than in other types of jaundice. This may be simply on the basis of duration of the jaundice, but itching may precede the jaundice.[146] Cases of long duration of jaundice before the diagnosis of carcinoma was made have also been reported, one and three-quarter years in one instance,[216] two years in another,[65] and three years in a third case.[201]

Weight loss is the most common finding (about 90 per cent) although not usually the first,[6,41,65,165] and it does not bring many patients to the doctor. Weight loss in carcinoma of the pancreas is extreme, frequently averaging more than 5 pounds per month. As much as 84 pounds were lost by a patient in one case before jaundice developed.[41]

Weight loss is greater with carcinoma of the pancreas, because of longer duration before onset of jaundice, than with carcinoma of the papilla of Vater, since jaundice usually brings the patient to definitive treatment. The average duration of symptoms in carcinoma of the pancreas is 4.6 to nine months as compared to nine to eleven weeks with carcinoma of the ampulla of Vater.[77,178,207,263,177] Weight loss in carcinoma of the head of the pancreas is not significantly different from loss of weight in carcinoma of the body and tail. It is intriguing to compare this with the failure of children with chronic cystic fibrosis of the pancreas to gain weight.[24,248] It does not seem to be closely related with pain, as does the weight loss in late chronic pancreatitis in which pain prevents adequate alimentation.[3] Weakness is always associated and may be extreme.

Non-specific *gastrointestinal symptoms* such as anorexia, nausea and vomiting cannot be said to be related particularly to carcinoma of the pancreas but they are very common complaints. An aversion for or complete rejection of food rather than true anorexia is considered distinctive of cancer of the pancreas.[310] A feeling of gastric fullness and flatulence is general.[35,50,163] This may be related to the very high incidence of achlorhydria, which occurs in 40 per cent to 58 per cent of patients with carcinoma of the pancreas.[6,35,163]

Vomiting is not rare.[50] Strangely enough, it has been reported to occur more frequently with carcinoma of the papilla (40 per cent) than with carcinoma of the pancreas (14.8 per cent).[207] This may be related to the increased frequency of cholangitis, chills and fever with the papilla lesions. Nausea, especially in the morning, has been observed as a specific complaint.[18,163]

Diarrhea, which may or may not be associated with steatorrhea, has been reported as the only symptom in cases of pancreatic malignancy.[257] It has been observed in 14.8 per cent of cases. The diagnosis of pancreatic malignancy should be seriously considered and ruled out in elderly patients with unexplained diarrhea.[35,50,110,163] Constipation, first noted by Cordua, is more common according to some reports[18,19,272] but obviously would not be as significant since it is so usual in this age group.

Especially *bulky stools* are frequent in pancreatic disease and carcinoma is no exception, as was observed fifty years ago.[114,239] This increased bulk is due primarily to undigested fat and protein. At times the steatorrhea is ob-

vious.[163,313,317] It may be an early sign of cancer.[41] Latent steatorrhea may be determined by careful tests for fat in the stools or by force-feeding of fat, and will be found in 22.2 per cent of cases.[227]

Creatorrhea is also seen in fairly obvious form, with undigested muscle fibers in occasional cases.[114] Careful microscopic examination will determine their presence, in as many as 18 per cent in one series.[41] Test diets such as that of Nothman[227] are of value in producing evidence of steatorrhea and creatorrhea in pancreatic disease.

Bleeding into the gastrointestinal tract, as indicated by occult blood, is noted in 25 to 37 per cent of patients tested.[69,80,121,163,215,231,317] Blood in the stools is especially frequent in lesions involving the stomach or duodenum, with ulceration, and in papilla carcinoma.[35,69] Ulceration has been observed in 50 per cent of cases of papilla, 33.3 per cent of pancreatic and 100 per cent of duodenal (periampullary) carcinomas.[208] Malignant ulcers simulating peptic ulcer have been seen in 11 to 37.5 per cent in reported series.[204,294] Severe gastrointestinal hemorrhage may be the initial symptom and may be repeated and occasionally fatal.[69,121,131,178,196,215,221,271,294,310]

Acute *cholecystitis* may be the first indication of carcinoma of this area,[278] and in patients of the older age group carcinoma should always be considered.[317] This complication might give the surgeon an opportunity to make the diagnosis but it is usually not considered. In one series in which cholecystitis occurred in eight of ninety subjects the malignancy was not discovered until a few days to twelve weeks later.[278] The operator felt an abnormality in the head of the pancreas in only two of the eight subjects, and failed to make the diagnosis in any.

Thrombophlebitis or phlebothrombosis, especially with multiple thromboses of the migrating type, has long been considered a frequent symptom of carcinoma of the pancreas.[103,124,161,179,189,300,309,310] Trousseau[315] is said to have been the first to note this phenomenon. Thromboses should certainly lead one to consider this diagnosis in all patients even without symptoms[102,124,161,189,300] or signs of pancreatic disease.[119,152,179,283,288] It has been the first symptom in some cases.[309,318] This is especially important since thrombosis is much more common with cancer of the body and tail of the pancreas (50 per cent) than with lesions arising in the head (10 to 20 per cent),[204,300] and lesions of the body and tail often are asymptomatic even to death.[31] This differential point is more obvious with multiple thrombi, the ratio in such cases being 31.3 per cent tail and body of the pancreas[161] to 9.7 per cent head.[300] Even before the time of antibiotics cancer was found to be second only to inflammatory disease as a cause of thrombosis,[93] middle ear infections alone being more frequent in one series.[136] In a group of fifty-eight cases of non-infectious diseases associated with thrombosis twenty-seven were patients with carcinoma.[12] Tumors arising from the lung and pancreas seem to be the most common in this regard.[70,130,251,311,318] Benign lesions of the pancreas and metastatic carcinoma of the pancreas[161] are associated with thrombosis infrequently and the thromboses rarely are multiple. It is noteworthy that multiple thrombosis seems to be infrequent in patients with jaundice.[300]

Emotional disturbances, especially depression and anxiety, are said to be unusually common with carcinoma of the pancreas. These may be early manifestations, and such patients have been admitted to mental institutions,[179,250,293,313,338] an unfortunate error. Characteristically there is anxiety, obstinate insomnia and conviction of imminent danger without a feeling of unreality or distortion of orientation. Personal experience and discussion with other surgeons lead this author to the opinion that these manifestations may be the result of failure of the physician to make the correct diagnosis in patients with symptoms such as pain and they are by exclusion labeled as psychosomatic. One such patient seen in three excellent hospitals because of undiagnosed abdominal pain, with completely negative studies, was considered a serious psychiatric problem and received psychotherapy until jaundice developed and on exploration she was found to have advanced disease.[65]

Diabetes is more common in carcinoma of the pancreas than in the general population, especially when extensive tumor involvement is present.[267,272] It is reported in 10 to 13 per cent, (6,205) and glycosuria has been found in 25 per cent of patients (78,249) with carcinoma of the pancreas. It has also been stated that cancer of the pancreas is six to ten times more common in diabetic persons than in the general population.[195] Of 256 patients with carcinoma and diabetes, 13 per cent had pancreatic carcinoma, six times the normal ratio.[195] If the diabetes is

not apparent, a diabetic curve will be found with the glucose tolerance test in 78 to 86 per cent of cases.[19,40]

Chills and fever may occur in as many as 50 per cent of patients with ampullary or papillary lesions but in only about 2 per cent of patients with lesions of the pancreas.[196,207,231] Jaundice and cholangitis are expected with these complaints and a gallbladder colic type of pain is frequently associated.[231] In the past, multiple abscesses of the liver were frequently found in these patients at postmortem or at operation, and they still occur.[61,131] Low grade fever was observed in nineteen of thirty-three patients and an elevated white blood cell count in a high percentage of cases.[163]

PHYSICAL EXAMINATION

The abnormal findings most commonly noted on physical examination are an enlarged liver, frequently hard, a distended gallbladder, tenderness or resistence in the upper part of the abdomen and a mass in the region of the pancreas. (Table VI.) Palpable enlargement of the liver is observed in 50 to 65 per cent of cases.[65,105,178,207,208,310] Enlargement is not always due, as may be thought, to the presence of metastases but rather to distention of the liver and cholangitis,[317] and/or fatty infiltration secondary to deficiency of lipotropic substance found to follow pancreatic deficiency.[33,212,252,268] Such hepatic enlargement alone therefore should not preclude operation.[65,207,286] Enlargement of the liver is more common with carcinoma of the head, 77.3 per cent, than with carcinoma of the papilla, 66.6 per cent, in the presence of icterus.[207,208] When present, metastases from carcinoma of the pancreas or the ampullary region are usually small.[11,163] Large masses in the liver are not necessarily metastases but may be benign lesions such as retention cysts.[55]

The gallbladder is enlarged to palpation in about 50 per cent of patients with jaundice.[18,41,65,77,163,178,207] Even in the non-icteric patients it is palpable in a significant number of cases.[105] At operation or postmortem the incidence of distended gallbladder has been found to be in the neighborhood of 90 per cent.[77,115,178,203,215] In contrast, patients with jaundice and chronic pancreatitis were found to have a distended gallbladder in only 15 per cent of cases,[115] and the incidence is even lower with common duct stones, as expected from Courvoisier's law.[75]

Recent reports have stressed the large number of patients with associated gallbladder disease, varying from 15 to 52 per cent.[19,105,196,204,215,264,268,272,278] Stones were found in about 20 per cent and common duct stones in 5 per cent of patients in one series.[204] The danger in this coincidence is of course that the surgeon will be satisfied with the diagnosis of stone and miss the perhaps early carcinoma of the pancreas. Hydrops of the gallbladder also occurs in a significant number of patients with common duct stones,[100,163] in opposition to Courvoisier's law, so that this finding cannot be used as an absolute diagnostic sign. The use of curettings from the common duct for microscopic analysis has been shown to be diagnostic[323] and should be of value in patients with stone in whom there is difficulty in entering the duodenum.

TABLE VI

	Total Cases	Liver	Gall-bladder	Mass	None
Cliffton[65]	122	66	26	18	22
Brown et al.[41]	92	44	15	Few	..
Arkin, Weisberg[6]	75	Mass	50%	....	..
Kiefer[163]	33	15	15	9	..
Ecklin[100]	139	1	121	....	..
Miller et al.[203]	...	68%	.....	14.8	..
	...	52%	.....	10	..
Futcher[115]	31	....	.....	12	..
DaCosta[78]	37	....	.....	13	..
Moore, Younghusband[215]	...	63%	.....	....	..

Stenosis of the terminal common duct or fibrosis of the sphincter of Oddi and papilla and other benign conditions such as pancreatitis may mimic carcinoma of the papilla, and so are also diagnostic problems, both preoperatively and at operation.[53,115,246,261]

The finding of a mass in the region of the pancreas itself was much more common in the early series of patients,[72,76,112,118] possibly because this was the only means of making the diagnosis. At present it is observed in approximately 20 to 30 per cent of patients and these are usually but not always far advanced.[18,65,77,163,208,310] These masses are frequently tender. (310, personal observation).

Splenomegaly may occur secondary to compression or thrombosis of the splenic vein.[98]

Ascites is uncommon except as a late manifestation in carcinoma of the pancreas.[19,163,310] When present ascites is due in most instances to peritoneal seeding but it may follow obstruction of the venous return by lymph nodes, hepatic

metastases or thrombosis.[19] Edema of the legs occurs even less commonly.

LABORATORY METHODS

X-ray examination is of value in arriving at the correct diagnosis[266] but cannot be said to be of great value in the early case, although operable cases have been diagnosed by x-ray.[17,65,107] The correct diagnosis is made in about 40 to 50 per cent of the cases.[17,40,107,141] Changes in the mucosal pattern and rigidity may occur with invasion of the duodenal wall, even without mucosal ulceration.[71,141] Abnormalities of motor activity of the small bowel are even earlier manifestations.[17,141]

The signs most frequently found to be helpful are the inverted S sign of Frostberg,[117] the pad sign of Case[52] and a defect due to the dilated common duct or gallbladder.[42,52,141] Circumscribed filling defects or displacement of the colon or stomach may also be observed.[104,141] The frequency of ulceration of the duodenum and stomach with carcinoma of the pancreas sometimes may lead to a false diagnosis of ulcer.[204,207] The finding of widening of the duodenal loop, frequently considered diagnostic and sought by the uninitiated, is almost always too late for satisfactory treatment.[107]

As might be expected from the position of the kidney in relation to the pancreas, displacement of this organ or of the ureter by the lesion, especially if it be in the tail, may be helpful in rare instances,[34,288] although other retroperitoneal tumors more frequently displace the ureter.[288]

Visualization of the common duct, especially by intravenous cholangiography in the nonjaundiced patient, might conceivably demonstrate displacement,[325] and aortography has been suggested as a means of distinguishing pancreatic from renal lesions and cysts from malignant tumors.[2] Perhaps the most promising technic for diagnosis is the combination of retroperitoneal air and tomograms called pneumostratigraphy.[120] Further evaluation of this is in progress. Cholangiography and pancreatography at operation are particularly valuable.[89,174]

Laboratory tests for use in diagnosis are very popular but do not seem to be of great value. Since Berk[20] and Dreiling and Janowitz[96] have given such excellent reviews of this subject it will be mentioned only briefly.

The tests of liver function in the presence of icterus are those typical of biliary tract obstruction. Serum and urinary lipase and amylase may be elevated in patients with early block of the pancreatic duct, as with carcinoma of the ampulla or duct of Wirsung,[207,228] but these enzymes may also be low in patients in whom the block has been prolonged with resultant destruction of the secreting pancreas, or involvement of much of the gland by tumor.[96] Stimulation of the gland by secretin or other drugs also gives equivocal results for the same reasons.[91,92,97,150,173,183,194,216,217,227,229]

The serum antithrombin test suggested as a diagnostic measure for cancer of the pancreas[147] and other tests of coagulability of blood[219,291,323] have not been found to be definitive.[94,95]

Duodenal drainage,[185] though a technically difficult procedure, is potentially of the greatest value and at present the only method available for obtaining a definitive diagnosis without surgery. Precise localization of an obstructive lesion is possible. If both biliary and pancreatic secretions are absent the obstruction must be in the head of the pancreas or the papilla of Vater. If the pancreatic and biliary flow are normal in volume the lesion must be hepatocellular, not obstructive. If the pancreatic secretions are ample despite biliary obstruction the lesion must be in the extrahepatic biliary system or there is an anomalous pancreatic duct, either a large duct of Santorini or other accessory ducts[171] or, less commonly, a separate entrance of bile duct and duct of Wirsung into the duodenum.[73,205,270]

With partial obstruction of the pancreatic duct there is a decrease in the quantity of bicarbonate and enzymes in the pancreatic secretion but the relative concentrations remain the same. With chronic pancreatitis, on the other hand, the quantity of pancreatic secretion is normal but there is a decrease in the concentration of bicarbonate and enzymes. The greatest reduction in the volume of pancreatic secretion in association with cancer, but without biliary obstruction, occurs in diffuse lesions.[95,96]

Duodenal drainage may also return blood which, in the presence of biliary obstruction and/or pancreatic duct obstruction, must be considered strongly suggestive of carcinoma.[63,68,328] Gross blood in the drainage has been reported in 25 per cent of patients with carcinoma of the head of the pancreas and with 38.4 per cent of ampullary carcinoma.[207] The study of duodenal juice for the presence of malignant cells by the Papanicolaou technic has not been universally satisfactory but diagnostic

successes have been reported.[175,190,279] A positive diagnosis or suspicion of the diagnosis has been obtained in eleven of twenty cases of carcinoma of the liver, biliary tract or pancreas, with no false positives in thirty-eight cases.[175] The smallest carcinoma giving a positive diagnosis was 2 cm. in diameter.[175] A positive smear has been obtained in one case from the T-tube drainage of the common bile duct, which would suggest such examinations of bile drainage in all patients with external drainage for obstructive jaundice.[190]

TREATMENT

Despite the disillusionment with resectional therapy for carcinoma of the pancreas in particular,[54,145,244,328,331] and less so for carcinoma of the ampullary region, surgical excision or short-circuiting remain the only method of cure or satisfactory palliation.

Radiation therapy may be helpful in palliation especially of pain but has offered no known cures for this disease.[226,253] Similar results have been reported previously[53] with an average survival of eight months in one series.[240] Survivals up to eighteen months have been recorded.[253] Treatment by surgery together with local radium has been reported in carcinoma of the papilla with extended survival.[1,319] The insertion or instillation of radioactive materials by fine tubes or threads at the time of surgery may offer advantage in the future.[133]

A hopeful note is found in postmortem statistics. Even at the time of death many tumors, especially those in the region of the ampulla or papilla of Vater, are found to be localized and technically resectable with the possibility of cure. As many as 75 per cent of 110 subjects with ampullary carcinoma were found to be without metastases in a series collected in 1913.[239] Even in series limited to carcinoma of the pancreas, obviously more difficult to diagnose and apparently more malignant, as many as 20 per cent have been found at postmortem to be free of apparent metastases and obviously resectable.[41,205]

The poor results in carcinoma of the pancreas and its immediate environs depend on several factors. The most serious defect is the inability to make an early diagnosis not only preoperatively but also at the time of operation. Bowden[30] and Carlson[50] referred to the difficulty of making the diagnosis at operation and this author missed a very small tumor involving the common duct found at postmortem to be an ideal case for resection.[65]

In any large series, cases have been missed at exploration and other cases have been proved finally by biopsy after prolonged procedures but then lost because of complications such as pancreatic fistula.[14,30] Even the pathologist when presented with the resected pancreas may miss the diagnosis, as in a case reported by this author.[65] Because of these difficulties and because of fear of spreading the cancer[245] it has been suggested that resection should be performed if the clinical evidence and surgical exploration confirms the diagnosis, without extensive attempts at biopsy.[55,812] Before this is done one should take advantage of the newer x-ray technics including: (1) cholangiogram by needle in the common duct, which might show the block due to tumor with characteristic irregularity and (2) retrograde pancreatic duct visualization by insertion of a polyethylene catheter,[89,173,174,302] since diagnosis of tumor blocking the duct of Wirsung has been made by this technic.[174]

Biopsy through the duodenum[236] or by a Silverman needle[164] may be justifiable and may offer more promise without danger of spread of the disease. There is always the possibility of resection of a benign lesion[28,30,51B,55,251,264] but this is less frequent and less serious than missing an early carcinoma, and has not occurred in at least two series.[65,82]

Pancreatectomy is said to have been successfully performed first in 1882 by Trendelenburg[313] for spindle cell sarcoma. Briggs[39] in 1890 resected a large sarcoma of the pancreas, with survival. Other early operations were by Biondi[22] and Terrier.[308]

In 1887 Kappeler[155] described the first successful cholecystjejunostomy, with survival over a year. It was in this same year that the first adenocarcinoma was successfully removed, through the loin, by Ruggi.[279A] Other successful resections of a carcinoma, of the tail, were by Cades[48A] in 1895 and, of the head, by Tricomi[314] in 1899. In 1906 Villar[322] was able to collect fifteen patients with resection of the pancreas for carcinoma, seven of whom survived operation. The first reported attempt at resection of the head of the pancreas, duodenum and a portion of the stomach, with only a twenty-four-day survival, was by Codivilla in 1898.[66]

An interesting successful resection of a tumor of the body of the pancreas with end-to-end

anastomosis was reported by Finney,[112] with a long term survival.[113]

In 1898 Halstead first removed a carcinoma of the papilla of Vater by a transduodenal excision, with survival for several months.[131,132] Other cases, by Rixford, Mayo and others, quickly followed.[201A,273]

The first resections of a cylindrical segment of the duodenum with the tumor and reimplantation of the ducts was by Mayo-Robson and Korte.[165,201] Tuffier[316A] in 1905 performed a more radical resection of part of the head of the pancreas with the papilla for carcinoma in a patient who had had a local excision of the papilla eighteen months previously. Neither of these patients survived, but Hirschel[140] in 1914 had a successful case in which the patient survived for one year.

In 1912 Kausch[158] carried out a procedure previously suggested by himself[157] very similar to the present technics with resection of the first and second parts of the duodenum and head of the pancreas, then implantation of the end of the remaining pancreas into the distal duodenum, gastroenterostomy and cholecystenterostomy in one stage. The patient succumbed to cholangitis three years later and at postmortem there was no evidence of cancer. Tenani[307] had a similar success with a two-stage procedure in 1922.

Desjardins[84] and Coffey[67] worked out and described the modern methods of pancreatectomy with reimplantation in animals but did not report any operations on patients. The modern period of surgery of the pancreas can be said to have followed the report of Whipple, Parsons and Mullens[331] who described their two stage pancreaticoduodenectomy with cholecystjejunostomy and gastrojejunostomy in 1937. Since then innumerable articles have been written on the subject of technic. These have been reviewed thoroughly in numerous surgical papers[45,58,59,81,85,87,88,123,186,192,236,237,249,269,280,301,326,331] and in books, including those by Brunschwig[43] and Cattell and Warren.[55] In essence, the chief differences are in regard to: (1) the type of biliary-intestinal anastomosis, (2) the necessity for implantation of the pancreas into the gastrointestinal tract, and (3) the relative positions and distances between the biliary intestinal anastomosis, the pancreaticoenterostomy and the gastroenterostomy. In summary, it would seem desirable when feasible, but not essential, to preserve pancreatic function for the gastrointestinal tract and to make a choledochojejunostomy at some distance above the gastroenterostomy[58,81A,244,249] in order to prevent or at least limit attacks of cholangitis. The choledochojejunostomy should be generous to prevent stricture, which is a serious complication. A one-stage procedure is favored except with certain contraindications.[55] Serious consideration has been given to more radical procedures such as wider resection about the head with inclusion of the superior mesenteric and portal veins or total pancreatectomy. Anatomic and pathologic data strongly support the desirability of the extensions. Even in the normal pancreas the superior mesenteric vessels, particularly the vein, are encircled by or actually covered by a thin layer of pancreas[110,170A,233,255,340] and so a total clean resection even of the normal head of the pancreas could not be performed without incising gland tissue. In the presence of cancer, the incised gland might contain a tumor. The lymphatic drainage also follows these vessels and the splenic vein very closely.[106] It is a common experience to find the tumor adherent to the portal vein[59,207] and many surgeons peel the tumor or inflamed gland off the portal vein, an obviously inadequate cancer operation even without pathologic evidence of tumor in the area. This is, of course, less common with carcinoma of the ampulla or papilla.[207]

That resection of the portal vein is feasible has been shown clinically.[81,185,197,215,254] Child has, in experimental animals and in three clinical cases, outlined the problems involved and demonstrated the feasibility of the procedure.[60,62]

Total pancreatectomy is indicated in many cases, perhaps ideally in all, because of the proved presence of tumor cells in the pancreatic ducts,[9] the instances of multiple tumors or seeding in the proximal (retained) pancreas,[244] and the pathologic demonstration of tumor in the periphery of the resected gland even in many cases of ampullary carcinoma.[207,215] Total pancreatectomy with survival was proved to be feasible as long ago as 1900[114B] and several cases have been reported since.[86,111,127,263,274] Physiologic studies[86,129,263,333] have shown amazingly good response to insulin, only 20 to 40 units being necessary in one case.[86]

The reasons for the relative frequency of a localized lesion at postmortem,[41,163,207] and the infrequent five-year cures, is difficult to determine. It is possible that small metastases which

would progress rapidly in the patient are missed at postmortem. The frequency with which malignant cells are left behind in apparently normal tissue is a second factor.[207] A third factor is the frequency of mortality from the surgical procedure itself, particularly as a result of cholangitis, occasionally of malnutrition. The former should be and appears to be less serious with modern chemotherapy, and adequate medical management should minimize the latter. The possibility of spread by the use of open biopsy must be kept in mind and it has been considered undesirable for this reason, among others.[30,50,55,82]

Conservative surgical procedures still have an important place in the treatment of these malignant tumors. These include biliary-intestinal anastomoses alone,[32,55,115] usually cholecyst- or choledocho- duodenostomy,[65,237,299] gastrostomy,[85,234,252,326] or jejunostomy,[58,155,299] and sometimes gastroenterostomy for the rare instance of duodenal obstruction by the tumor. Palliation with relief of jaundice and pain are usual, with prolonged survival compared to non-treated patients.[65,178] An occasional long-term survival has followed.[26,65,159] Certainly when in doubt it is indicated as a first-stage procedure. With obstruction of the pancreatic duct causing pancreatitis and poor digestive function, anastomoses of the pancreatic duct to the jejunum have been performed.[55] Even more satisfactory might be the technic of terminal or caudal pancreaticojejunostomy suggested recently for chronic pancreatitis with obstruction.[3,99A] Cholecystostomy alone does not seem to be a desirable procedure because of the distress of prolonged bile drainage and lack of significant survival. There is perhaps some room for debate concerning the abandonment of wide local excision of lesions of the papilla of Vater.[143,144,239] By wide duodenotomy excision of a large area of duodenal mucosa with the papilla, ampulla and surrounding pancreas can be effected with reimplantation of the ducts into the duodenum,[131,132,143] and this can be accomplished with a much lower mortality than the 31.1 per cent reported in the past.[143]

SURVIVAL

It has been stated in the past that a patient with carcinoma of the pancreatic area would live longer without operation,[188] and more recent pessimistic reports may have led physicians to return to this attitude.[54,244,328] Present statistics certainly do not support this contention.[43,54,55,65,163,178] The average survival after diagnosis without treatment is about three weeks to 2.5 months,[65,239,301] after radiation therapy eight months,[240] after palliative biliary-intestinal anastomosis 5.4 to 13.9 months,[65,151,301] and after excision surgery 10.5 to 25.8 months[65,186,301] The mortality for the various operations has varied remarkably.[55,59,65,301,331]

Hunt,[143] in his 1941 review of local excision of 109 patients with carcinoma of the papilla, reported an operative mortality of 31.1 per cent, and of the seventy-five survivors 41 per cent were reported to be living and well for one to nine years after operation. The longest survival period was twenty-two years and fourteen patients had survived from three to twenty-two years.

Radical pancreatoduodenectomy for carcinoma of the pancreas and periampullary region originally had a very high mortality, in early series 20 to 30 per cent.[13,58,81,182A,207,236,331] The mortality for carcinoma of the ampulla has been consistently lower than that for carcinoma of the pancreas.[54,55,207] More recent statistics have been much improved; in one series of 102 cases an over-all mortality rate of 12.7 per cent, with 17.3 per cent for the lesions of the pancreas and 6.6 per cent for ampullary or papilla lesions.[55] These figures have decreased even more in late years, in recent series to an over-all mortality rate as low as 7.3 per cent[55] and 8.3 per cent.[331]

The survival rate and duration is much greater for carcinoma of the ampullary region than for carcinoma of the head of the pancreas. Cattell and Warren[55] report three of ten (30 per cent) possible five-year survivors for ampullary carcinoma, and two of eighteen (11 per cent) of patients with carcinoma of the head of the pancreas living and well after five years. Of those with ampullary lesions two were surviving nine years and one ten years after resection. Miller and Clagett[207] reported two five-year survivors of carcinoma of the head of the pancreas. In one collected series of 150 patients with carcinoma of the head there were three five-year survivors and only nine were living more than eighteen months after operation.[62]

The most recent statement of five-year survivals recorded twenty-three instances,[82] eleven of carcinoma of the head of the pancreas and twelve of carcinoma of the ampulla. In their personal series Dennis and Varco had two of each surviving for five or more years from

twenty-three resected and forty-six total cases seen, a five-year survival rate of 21 per cent and 10.5 per cent, respectively.[82] In another group of thirty-seven cases, twenty-seven proved pathologically with eight resections, there were two five-year survivors, 5.1 per cent of the total cases, 7.4 per cent of the proved cases and 25 per cent of the resected cases. One of the patients with carcinoma of the head of the pancreas survived nine years, only to succumb to another disease, and at postmortem there was no evidence of cancer. Four additional cases of carcinoma of the head of the pancreas,[5] by Cattell and Warren,[55] Glenn and Hays,[121] Moore and Younghusband,[215] and Pratt and Welch,[260] and a case of ampullary carcinoma by Glenn and Hays[121] should be included.

Many patients who survived less than five years, who at postmortem showed no residual cancer, certainly were potentially cured patients.[61]

The reasons for the better survival from lesions of the papilla are obvious. These include: the lower incidence of vascular and perineural involvement (37 per cent and 60 per cent for carcinoma of the head of the pancreas and 6.6 per cent and 0 per cent for the ampullary lesions), the lower incidence of lymph node metastases (60 to 75 per cent for carcinoma of the head of the pancreas and 30 per cent for the ampulla) and invasion of the transected common duct in 15 per cent of the patients with lesions in the head of the pancreas compared to none with ampullary carcinoma.[207,208]

In summary, it seems logical to state that the results of treatment for carcinoma of the pancreas, and of papilla of Vater and periampullary area, are better than commonly realized but are still open to marked improvement. This improvement will depend upon early suspicion of the diagnosis followed quickly by adequate treatment. The possibility of carcinoma of the pancreas should be considered in all patients with persistent, unexplained abdominal pain accompanied by weight loss and weakness. Diarrhea developing in or beyond middle age without demonstrable cause, especially if associated with creatorrhea or steatorrhea, should arouse suspicion. Associated psychologic changes and aversion to food rather than simple anorexia should add to the suspicion. Of course those with jaundice should be immediately explored. The associated development of diabetes should strengthen the suspicion. Any such patient should be thoroughly examined as rapidly as possible and in particular should have duodenal drainage studies, if available, with adequate evaluation. With persistent symptoms early exploration is indicated. This should include mobilization of the pancreas, careful observation for ductal dilatation, cholangiogram, duodenotomy and retrograde visualization of the duct of Wirsung by contrast media, and biopsy through the duodenum if a tumor is palpable (needle biopsy may be desirable). If a distinct tumor is felt, resection should be performed. If the surgeon cannot satisfy himself as to the differentiation of pancreatitis from carcinoma, judgment will determine the justification for resection or palliative operation, probably with re-exploration after subsidence of the pancreatitis.

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Review

Renal Lesions and Acute Renal Failure in Pregnancy*

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ACUTE reduction of renal function is observed in pregnancy under a variety of circumstances. Frequently, the oliguria or anuria is of a transient nature lasting only a few hours or at most two to three days. This may characterize the reaction of the kidneys to a brief hypotensive episode or to a severe pregnancy toxemia. When decreased urine output persists beyond these limits, the condition must be regarded as acute renal failure and the patient will pursue a protracted clinical course resulting either in recovery, with or without permanent renal damage, or in death. Pregnancy is a major factor in the etiologic background of the general problem of acute renal failure, a fact which becomes self-evident in hospitals with special facilities to care for these patients. Some 20 to 40 per cent of cases of acute renal failure are associated with pregnancy complications. Stating it another way, in female patients with acute renal failure, about 50% are or have recently been pregnant.[1]

The purpose of this work is to survey and classify the kidney lesions associated with pregnancy, particularly those involved in acute renal failure. Although such pathology cannot be considered out of the context of obstetrical complications, the emphasis will be on the background, cause and development of the renal lesion and its significance in terms of immediate survival and residual renal damage. The role of pregnancy toxemia, whether complicated or not, in relation to adverse effects on the structure and function of the kidneys will be assessed. Considerations will be given to those aspects of pathogenesis which make renal complications preventable or, if not preventable, manageable. Inherent in this study is the fundamental question whether or not the kidney of a pregnant woman is more vulnerable to injury. Further, on review of the patient's history, can the clinician interpret the nature of the renal lesion in an individual with depressed renal function? As a practical corollary, it is possible to offer a prognosis of the chance of recovery and the likelihood of permanent renal damage?

Several cases are included in the survey in which renal lesions were found at autopsy but in which no significant decrease in urinary output had been noted clinically. These serve to illustrate the range of renal changes found in women dying while pregnant or in the puerperium.

MATERIAL

Anuria in this study is defined as a urinary output of 100 ml. or less for a twenty-four-hour period, or as prorated. Oliguria is defined as a urinary output of 100 to 400 ml. for any given twenty-four-hour period, or as prorated.

This report is based upon eighty cases of depressed renal function; death occurred in forty-nine and autopsies were performed on these patients. Of the latter number, thirty-nine were observed at the Boston Lying-in Hospital during the years 1931 to 1948 prior to the adoption of hemodialysis as a method of treatment. The ten remaining patients who died and the thirty-one patients who survived were cared for at the Peter Bent Brigham Hospital. During these years physicians in New England and elsewhere referred patients with acute renal failure to this

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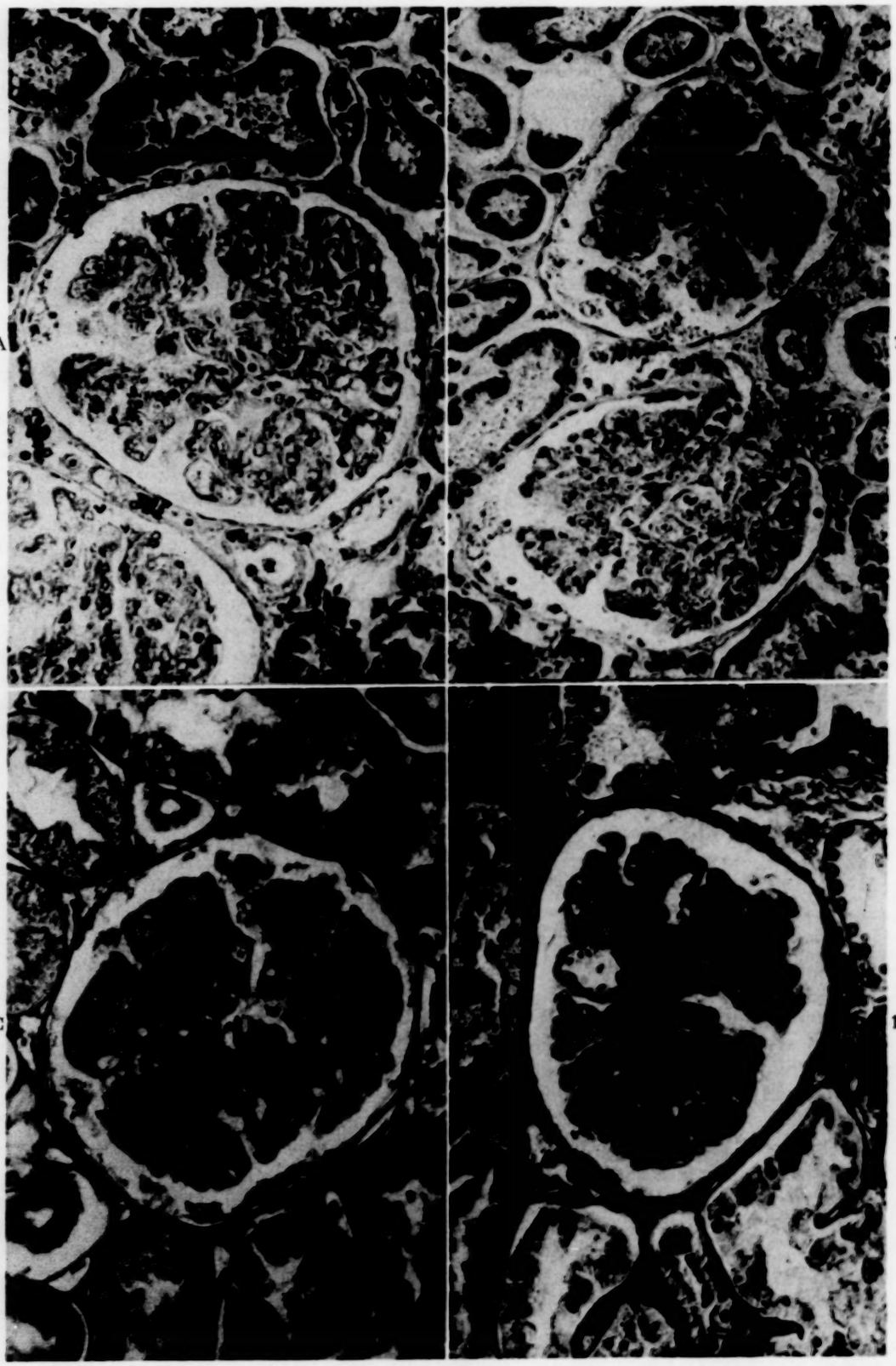


FIG. 1.

hospital for treatment because of the availability of a Kolff-Merrill artificial kidney for dialysis.

The fatal cases are classified anatomically in Table I. The non-fatal cases are clinically classified in Table II. Table III lists the ten fatal cases of the forty-one which were treated at the Peter Bent Brigham Hospital from 1948 to 1954, inclusive. The current mortality is 25 per cent.

Fatal Cases

Toxemia of Pregnancy. Severe toxemia was encountered in thirteen (26.5 per cent) of the fatal cases. With two exceptions, they were of the convulsive type. As far as can be determined, these were cases of unprovoked toxemia, that is, there was neither history nor physical nor laboratory findings to suggest antecedent glomerulo- or pyelonephritis, or cardiovascular renal disease. The majority of the patients (eight of thirteen) were primiparous. Five patients had anuria, but it is noteworthy that none had complete suppression of urinary excretion. In four of the five patients, the urinary output became markedly reduced shortly before the onset of convulsions. In the remaining patient anuria developed twelve hours prior to convulsions. The urinary output improved and increased steadily after delivery, but the patient died four days postpartum with severe aortic stenosis. Four of the patients with severe toxemia had oliguria which was limited to the acute phase of the illness and which disappeared promptly after the convulsive episodes had passed. In four patients there was no significant suppression of urinary output.

The renal lesion of convulsive toxemia has been studied by many writers since the original description by Fahr. In essence the kidney findings consist of thickening, reticulation and even splitting of the basement membrane of the glomerulus. (Fig. 1A.) Associated with this is the description of "swollen, ischemic" glomeruli, an observation so non-specific that it is meaningless. In an occasional case of fatal eclampsia, focal necrotizing arteriolitis usually in the afferent arteriole has been described. (Fig. 1B.) Lesions of the renal vascular tree commonly associated with hypertension, such as hyalinization of afferent arterioles or muscular hypertrophy of interlobular arteries, have been described in cases of toxemia in persons with a history of antecedent hypertension.

In the thirteen fatal cases of toxemia here cited, glomerular lesions were found in all. However, autopsies were performed in fifteen additional cases in which eclampsia occurred without reduced renal excretion. These were reviewed but are not included in this study. In none of these cases were convincing renal lesions of any type evident despite adequate routine sections and basement membrane stains. In other words, glomerular lesions were present in slightly less than 50 per cent of the cases of eclampsia in which autopsies were performed. Furthermore, in the thirteen cases in which lesions were identified, the most striking observation was that well over 90 per cent of the glomeruli were normal in appearance. Whatever changes were present were restricted to relatively few glomeruli, and even in the involved glomeruli, the histologic alterations were focal or segmental in distribution. In only two of the thirteen cases in this series, could one say that glomerular lesions were found with ease or with some frequency. (Figs. 1C and 1D.) Both of these cases exhibited necrotizing arteriolitis in an occasional afferent arteriole. In these cases, hypertension was known to have developed several weeks prior to death.

Tubular lesions are not a conspicuous feature in patients who die of uncomplicated toxemia of pregnancy. Not infrequently, "hyaline droplet degeneration" is described in tubular epithelial cells. In the present thirteen cases "hyaline droplets" were observed in eleven. (Fig. 2A.) Necrosis of tubular epithelium, cast formation or tubular rupture was not observed in any of the uncomplicated cases. The one exception to this was a case of toxemia, complicated by an episode of hemolysis, in which renal failure developed and the patient died of potassium intoxication. An element of hemorrhagic shock superimposed upon this patient's toxemia appears in the background but cannot be accurately documented. The details of this case are as follows:

Y. R., aged twenty-nine years, gravida I, Para I, was referred because of postpartum anuria. From the patient's history it appeared that the pregnancy had been normal and uneventful until the thirty-second

FIG. 1. Convulsive toxemia. A, glomerulus showing thickening of the basement membrane focally distributed in peripheral loops; hematoxylin and eosin, × 300. B, the glomeruli are normal. An arteriole shows segmental "smudgy" necrosis of its wall; hematoxylin and eosin, × 125. C, the basement membrane of most of the capillary loops are of normal thickness. One capillary loop shows pronounced thickening of the basement membrane; periodic acid stain, × 300. D, there is diffuse thickening of the basement membrane of the entire glomerulus; periodic acid stain, × 300.

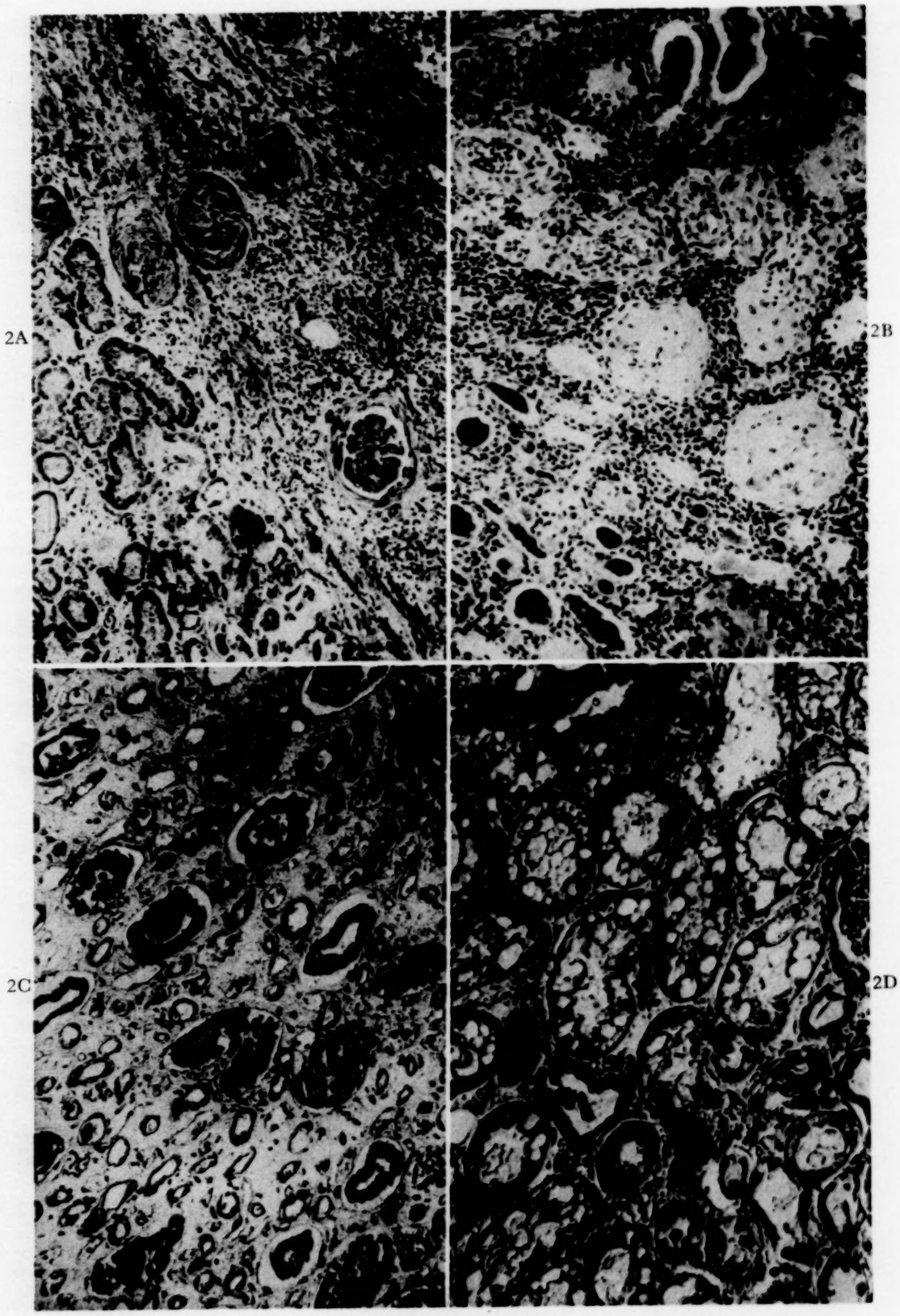


FIG. 2.

gestational week. Her course then became complicated by the insidious onset of edema involving ankles, hands and face. The patient was locally hospitalized the following week when the blood pressure rose to 210 systolic and 120 diastolic and was associated with intermittent vomiting. Three days after admission oliguria developed and failed to improve despite a conservative regimen of fluid and salt restriction. Induction of labor by amniotomy was performed successfully and spontaneous pelvic delivery occurred in the thirty-third gestational week. The delivery was complicated by postpartum hemorrhage. However, the record is not clear as to whether the hemorrhage was severe or not and exactly what therapeutic measures were instituted. The puerperium was complicated by many convulsions, vomiting and a persistent decline in urinary output.

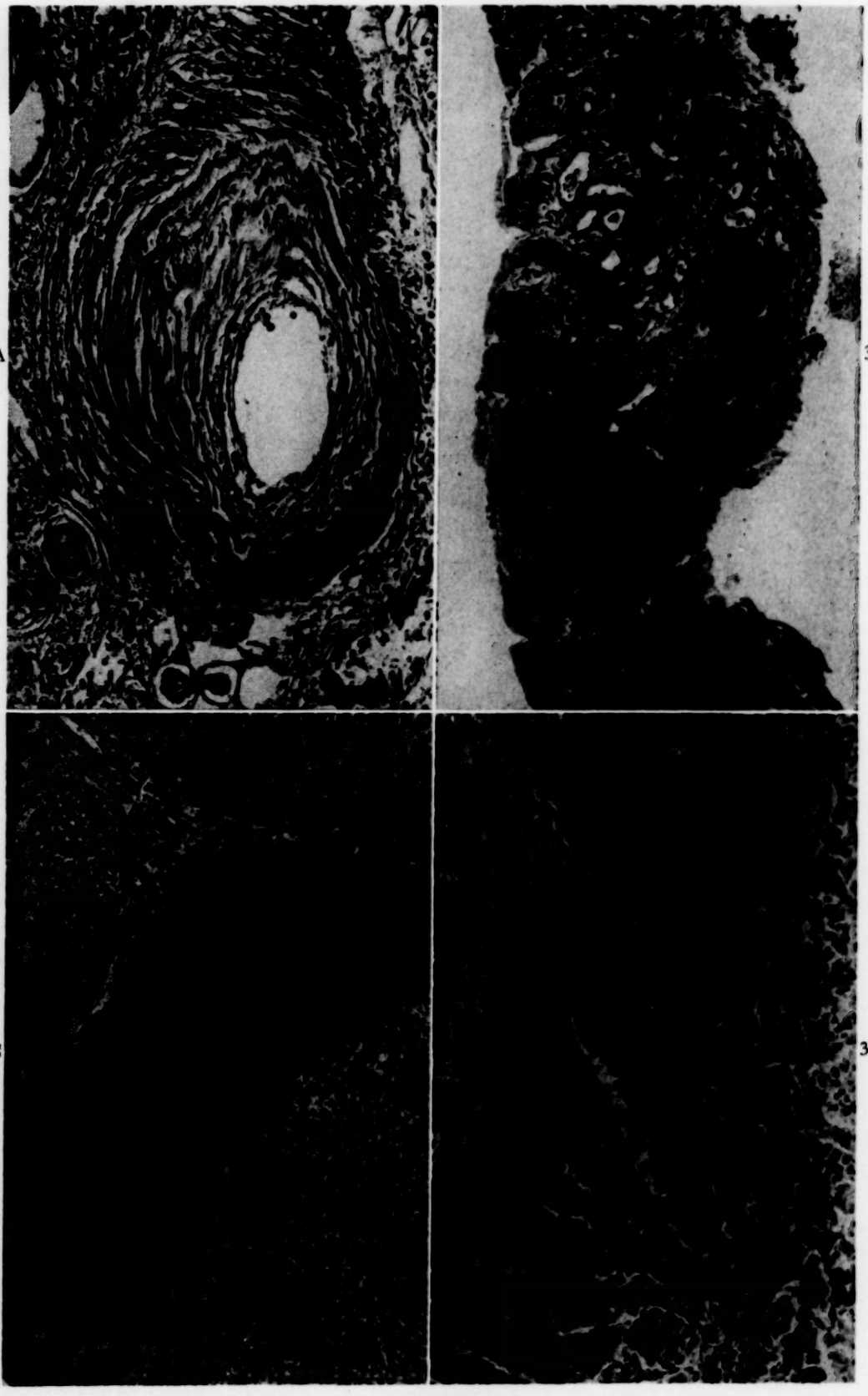
The patient was admitted to the Peter Bent Brigham Hospital on the second postpartum day. Physical examination revealed an acutely ill, edematous woman. There was no evidence of pulmonary edema. The heart sounds were normal. Other physical findings except for the edema were not noteworthy. Admission blood chemistry determinations revealed a blood urea nitrogen of 126 mg./100 ml., sodium 139 mEq./L., potassium 6.0 mEq./L. and calcium 4.0 mEq./L. The initial electrocardiogram was normal. The blood potassium rose slowly to 6.4 mEq./L., then to 7.0 mEq./L. Two days after admission the peripheral reflexes were somewhat diminished and the electrocardiogram showed changes consistent with early hyperkalemia. Dialysis with the artificial kidney was considered at this time. However, because of the potential dangers of heparinization in a recent postpartum patient, it was deferred. Unfortunately, within a matter of two hours marked gross cardiac arrhythmia and electrocardiographic disintegration characteristic of advanced hyperkalemia occurred in the patient. She died within approximately forty minutes on the fifth postpartum day.

Postmortem examination revealed that the right kidney weighed 220 gm. and the left kidney weighed 240 gm. The capsular surface was smooth and the consistency of the kidneys was firm. On section, the cortex was congested and separated from a pale medulla by a distinct zone of pallor at the cortico-medullary junction. Microscopic examination revealed heme casts and albumin casts in the tubules in the medulla as well as granular albuminous precipitate in the tubules of the cortex. (Fig. 2B.) Actual tubular necrosis was slight and scattered. Focal infiltrates of lymphocytes and eosinophiles were present in the interstitial tissues of the medulla and a few instances of tubulorrhexis were seen. The glomeruli did not show changes consistent with eclampsia. The liver weighed 1,820 gm. and was firm with a tense capsule. The liver surface was mottled with reddish areas of hemorrhage and the cut surface revealed these hemorrhages to be irregular and confluent, a few grayish yellow areas of non-hemorrhagic necrosis were also seen. Approximately one-third of the liver was so damaged. (Figs. 2C and D.)

The clinical sequence was acute severe toxemia, postpartum hemorrhage and convulsions with anuria. As the result of extensive acute hepatic necrosis and hemolysis, the patient died of rapidly progressing potassium intoxication which caused cardiac arrest although the urinary output was increasing at the time. A hemolytic crisis has been observed on rare occasions in pregnancy toxemia and from recent reports[2] it is evident that such patients can die with acute tubular necrosis. Although the mechanism of the hemolysis is unknown, this patient, in common with those reported, had extensive necrosis of the liver.[2]

Bilateral Symmetrical Cortical Necrosis of the Kidneys. The first authentic example of this dramatic lesion was reported by Juhel-Rénoy[3] in 1886. A subsequent report by Bradford and Lawrence[4] confirmed Juhel-Rénoy's observations and pointed out the presence of extensive "endarteritis" of the major renal vessels in the non-necrotic portions of the kidney, an observation which assumes significance in the light of the present study. Bilateral cortical necrosis of the kidney is not entirely restricted to pregnant women who have sustained uteroplacental apoplexy. Although about 80 per cent of the reported cases occur in association with this latter condition, the remainder are seen at random in adult males, non-pregnant women and in infants following a variety of etiologic backgrounds but notably associated with sepsis in some form.

FIG. 2. A, pyelonephritis. A portion of a wedge-shaped cortical scar showing destruction of renal substance, infiltration by lymphocytes and plasma cells and various stages of periglomerular fibrosis; hematoxylin and eosin, × 75. B, pyelonephritis. An end point of the lesion. Complete hyalinization of glomeruli thickening of vessels, colloid casts in atrophic tubules and a heavy inflammatory exudate are all present; hematoxylin and eosin, × 75. C, toxemia of pregnancy complicated by acute tubular necrosis. Severe hemorrhage developed following pelvic delivery at the thirty-third week. There was no uteroplacental apoplexy. The patient died with anuria and uremia. The photomicrograph illustrated the heme casts found in many of the renal tubules. No glomerular lesions were found; hematoxylin and eosin, × 150. D, hyperemesis gravidarum. High power view of proximal convoluted tubules showing cytoplasmic vacuolation. Presumably this lesion reflects depletion of body potassium. It is currently fashionable to call this "hypokalemic vacuolar nephropathy;" hematoxylin and eosin, × 225.



3A 3B 3C 3D

FIG. 3.

The usual clinical sequence of events in cases of renal cortical necrosis in pregnancy is fairly characteristic: extensive abruptio placentae, delivery of a stillborn infant, varying degrees of hypotension, anuria, uremia and generally death in seven to fourteen days. It is only with some reservation that the diagnosis can be made short of autopsy. However, a well-documented case report by Crook[5] indicates that not only can the diagnosis be made by biopsy of the kidneys (in this instance at the time of surgical decapsulation of the kidneys), but that recovery is possible!*

In the present series there were seven cases of anuria in which renal cortical necrosis was evident. All showed extensive areas of bilateral necrosis and all proved fatal. In view of the fact that this communication deals with the anurias and oligurias associated with pregnancy, it is not surprising that in all seven cases there was a history of toxemia complicated by abruptio placentae. The clinical features of these cases are summarized in Table IV, while the findings at autopsy are presented in Table V. In two of these fatalities, hemodialysis was performed. A more detailed abstract of the history of one case is herewith included.

CASE VI. This twenty-two year old gravida IV, Para III, was admitted on the sixth postpartum day from an out-of-state hospital because of oliguria, azotemia and pulmonary edema. There was no known history of previous renal disease but the patient had been hypertensive between pregnancies.

The first pregnancy, complicated by hypertension, albuminuria and edema, terminated in a premature delivery of a viable baby. The second pregnancy ended in a spontaneous abortion at two and one-half months. The third pregnancy eventuated in premature separation of the placenta at seven months with the delivery of a dead baby.

The fourth and present pregnancy resulted in premature separation of the placenta followed by delivery of a dead baby. No shock was noted clinically at the time, nor was jaundice observed. Following delivery anguria developed (renal output of less than 100 ml./day) and the patient's blood non-protein nitrogen rose to over 100 mg./100 ml.

On admission, the blood pressure was 176/100. On physical examination the heart was enlarged and there was a pericardial friction rub. Signs and symptoms of pulmonary edema were present. The liver was palpable three fingers below the costal margin. The urine showed 4-plus albumin, the sediment contained 20 to 30 white blood cells per high power field,

* Recently, two cases of renal cortical necrosis in which needle aspiration biopsy of the kidney was performed during life have come to our attention. In the first case (which we mention through the courtesy of Doctors William Caton and Walter Sheldon of the Grady Memorial Hospital, Atlanta, Georgia) the patient recovered. (Fig. 4B.) In the second case (courtesy of Doctor Gustave J. Dammin, Peter Bent Brigham Hospital, Boston, Mass.) the patient died. Interpretation of small biopsy specimens of the kidneys is fraught with uncertainty. Were it not for the insight afforded by Sheehan and Moore[34] to the effect that cortical necrosis is not always generalized and diffuse, it would be difficult to discriminate among the three cases mentioned in which biopsies were performed. However, in the two cases in which the patients recovered, the cortical necrosis was focal in nature. In the fatal case, the tissue aspirated showed only necrotic cortical tissue, compatible with the observation at autopsy of a diffuse, generalized necrosis. Through the courtesy of Doctor Arnold J. Rawson, Norfolk General Hospital, Norfolk, Va., we have had the opportunity to study the pathological material in a case of renal cortical necrosis which developed in a thirty-three year old woman who had suffered from Cushing's disease with sustained hypertension for ten years. Unknown to herself or her physician pregnancy occurred and following seven months of amenorrhea the patient was admitted to the hospital with signs and symptoms of a cerebrovascular accident. Five days later the patient suddenly went into labor and rapidly delivered a living premature infant. There was no overt evidence of premature placental separation. Following delivery, the patient was in shock and anuric. She died on the second day following delivery with a rising plasma non-protein nitrogen and a falling CO_2 combining power. Autopsy disclosed the cause of death was cerebral hemorrhage. There was a basophilic adenoma of the pituitary. The liver showed extensive areas of hemorrhagic necrosis. The heart weighed 400 gm. and was concentrically enlarged. The kidneys weighed 240 gm. and 220 gm. respectively and were the seat of typical patchy areas of cortical necrosis. The arterial tree of the kidneys showed the effects of hypertension of long duration with pronounced intimal thickening of the vessels as well as moderate medial hypertrophy. Thrombi composed of fibrin and platelets were present in a few of the interlobular arteries.

FIG. 3. A, Case V, a thirty-seven year old woman with bilateral symmetric renal cortical necrosis. The sclerosis of arcuate arteries has progressed to intimal hyalinization in this artery; hematoxylin and eosin, × 175. B, same case. Low power view of a needle biopsy showing the characteristic coagulation necrosis of glomeruli and tubules as well as interstitial infiltration; hematoxylin and eosin, × 90. (Courtesy of Drs. William Caton and Walter H. Sheldon.) C, Case IV a thirty-two year old woman with bilateral symmetric renal cortical necrosis. The liver shows extensive necrosis, both hemorrhagic and coagulation types. It is inferred that the rapid rise in serum potassium was influenced by this destruction of liver cells; hemotoxylin and eosin, × 40. D, Case II, a forty year old woman with bilateral symmetric cortical necrosis. The pituitary showed partial infarction necrosis. This high power view shows a fibrin thrombus in a sinusoid between the zone of infarction and the spared parenchyma; hematoxylin and eosin, × 300.



FIG. 4. Case 1, a thirty-three year old woman with bilateral symmetric renal cortical necrosis. Low power view showing the extent of gross necrosis. Note the spared zones beneath the capsule and at the cortico-medullary junction. Note also the thrombosis of interlobar and interlobular arteries. (This photomicrograph was taken by Dr. Arthur T. Hertig who has graciously permitted the authors to publish it.)

and many granular casts. The blood urea nitrogen was 90 mg./100 ml., CO_2 12.2 mEq./L., Na 145 mEq./L., K 5.2 mEq./L. and Cl 111 mEq./L., respectively. The patient was treated with penicillin, testosterone, digitalis and a balanced fluid intake. Dialysis was performed on the seventh and ninth hospital days (thirteenth and fifteenth postpartum days). The second dialysis resulted in a fall of blood urea nitrogen from 225 mg. per cent to 47 mg. per cent, the K from 6.8 mEq./L. to 6.0 mEq./L. and a rise in the CO_2 from 8.0 to 18.3 mEq./L. Despite chemical improvement, pulmonary edema persisted and the patient died on the sixteenth postpartum day.

In summary, in this group of seven multiparous patients with renal cortical necrosis

the renal lesion developed in all following toxic separation of the placenta. Five of the patients were over thirty years old; two were in the twenties. During the final pregnancies, hypertension and albuminuria had developed in all. Six of the patients had no history of toxemia in previous pregnancies while one had several toxemic pregnancies. The status of blood pressures could not be ascertained between pregnancies or in the early weeks of the present pregnancy except in two patients who were known to be hypertensive. Six of the patients survived from seven to sixteen days following delivery. The seventh patient survived only little more than one day, dying with electrocardiographic changes consistent with acute hyperpotassemia, presumably secondary to massive necrosis of liver parenchyma. In addition to this case, only one other patient showed necroses in the liver at autopsy and these were focal. The pituitary showed necroses in three patients; in two of these it was extensive ischemic necrosis without demonstrable thrombosis; in one patient the hypophyseal necrosis was focal and associated with small fibrin-platelet thrombi in the sinusoids. (Figs. 3 and 4.)

The renal cortical necrosis was bilateral and symmetrical in all cases. In four cases, the necrosis was "gross" as classified by Sheehan and Moore's[34] criteria; in the other three cases, it was "confluent patchy" involving more than 75 per cent of the renal cortex. Apart from this slight quantitative difference, there was no significant qualitative difference among the seven cases. In each case there was extensive thrombosis of the renal arterial tree; the thrombi contained fibrin, platelets and entrapped red and white blood cells. The thrombosis was chiefly in the interlobular and interlobar arteries but the process could be seen in the afferent arterioles and occasionally in loops of the glomerular tuft. There was no morphologic evidence to support the notion that the thrombotic process was initiated in the afferent arteriole and underwent retrograde propagation. Likewise, there was no conspicuous necrosis of the media of vessels in which thrombi were present, except to a limited extent in the middle of zones of the most intense ischemic infarction. The primary process in the kidney was one of ischemic coagulation necrosis of all elements in the cortex as a consequence of the arterial thromboses. Secondary effects were noted in the medullary tubules as well as in the limited zones of spared cortical tissue. *In every case there was a degree of nephrosclerosis in the arcuate and interlobar arteries proximal to the segments in which thrombosis had occurred.* In three cases this arteriosclerosis was moderate, in one case moderate to marked and in the remaining three cases pronounced. In all cases the sclerotic process consisted of intimal thickening, fibrosis and hyalinization with reduction of the caliber of these vessels; the process was diffuse and not merely found at random. In two of the cases of renal arteriosclerosis classified as "moderate," the women were twenty-two and twenty-five years old respectively; for women in this age group, such arteriosclerotic changes must be construed as advanced in relation to their age. In two of the cases classified as "pronounced," the women were in their late thirties and the lesions would be considered advanced even for much older women. We interpret this type of renal arteriosclerosis as the morphologic background upon which cortical necrosis is more likely to develop following abruptio placentae than where the renal arterial tree is considered normal. (Figs. 5 and 6.)

Acute Tubular Necrosis. Of forty-nine fatal cases, nine patients (18 per cent) died with lesions restricted to the renal tubular epithelium. These lesions are similar to those described by Lucké[6] as "lower nephron nephrosis," and by Bull et al[1] and Oliver[7] as "acute tubular necrosis." In this discussion we employ the latter term because the destruction of tubular epithelium is not of necessity confined to the lower portion of the nephron, nor is the term "nephrosis" indicative of the nature of the cellular lesion. Eight of the nine patients were anuric at some time during their clinical course; one patient was oliguric and is classified in the miscellaneous group in Table I.

A brief survey of the history of these cases indicates that in all instances there was an episode of hypotension, usually a consequence of hemorrhage or intravascular hemolysis which preceded the development of renal failure and which in some instances was an unfortunate extraneous complication of the therapy employed rather than an inherent complication of the pregnancy itself. (Table VI.)

In summary, the common denominator in these nine cases of acute tubular necrosis was shock, due to extensive hemorrhage, intravascular hemolysis or severe sepsis. In only one case was toxemia a feature. Massive, sudden intravascular hemolysis was encountered in

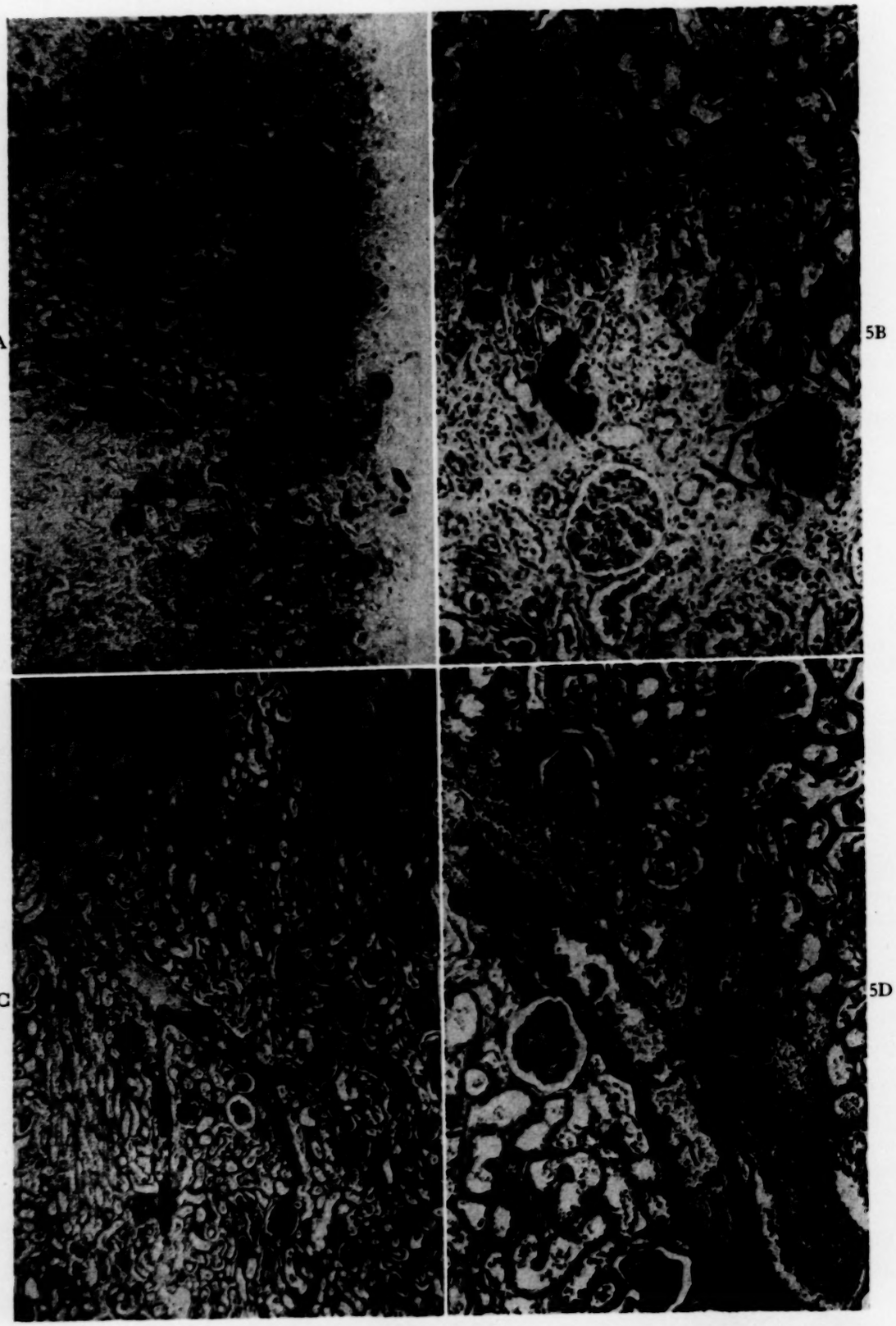


FIG. 5.

three patients while severe external hemorrhage involved five cases. Shock was associated with one case of peritonitis. (Fig. 7.)

Pyelonephritis. In this category, we have included a variety of renal infections. Of the forty-nine fatal cases, eight patients had pyelonephritis, three of these were associated with oliguria and five were without significant depression of renal output. It would appear that the absence of oliguria does not serve, in pregnancy, to differentiate between patients with pre-existing chronic pyelonephritis from those with an acute initial infection of the kidneys.

Three patients exhibited an acute hematogenous infection from E. coli, streptococcus and B. welchii, respectively, followed by an inhibition of renal function. Death intervened in three to eight days as the consequence of overwhelming bacteremia. The acute depression in urine output was attributed to a diminished renal reserve in the presence of serious infection and was not primarily associated with underlying glomerular or tubular disease. In only one of the five patients who died, without significant depression of renal output, could the renal lesion be considered the cause of death. Furthermore, in only two of the five patients, were the renal findings morphologically comparable to those described by Weiss and Parker[8] in their description of chronic pyelonephritis. The renal lesions noted in the remainder of the patients were purely incidental playing no important part in the clinical picture. Although these deaths occurred in the era prior to effective antibiotic therapy, they emphasize the inherent risk of severe renal infection in the pregnant woman. Chronicity of pyelonephritis and its tendency to recur and exacerbate are known obvious features. Less obvious is the fact that such cases in pregnancy are rarely diagnosed correctly until the patient is severely ill. The pathologic nature of long standing chronic pyelonephritis encountered in two cases in which no abnormality of kidney function was demonstrable can be seen in Figures 5A and B. The latter is from a case in which the left kidney weighed but 25 gm. and in which the entire renal parenchyma was completely destroyed. The right kidney weighed 150 gm. and also showed extensive chronic pyelonephritis, but an occasional functioning nephron unit could be seen. (Figs. 6A and B.)

TABLE I

FATAL CASES OF DEPRESSED RENAL FUNCTION

I. Patients with Anuria	
Acute tubular necrosis	8
Bilateral renal cortical necrosis	7
Convulsive toxemia	5
Miscellaneous	4
	24
II. Patients with Oliguria	
Pyelonephritis	3
Convulsive toxemia	4
Acute tubular necrosis	1
Miscellaneous	2
	10
III. Patients with No Decreased Urinary Output	
Pyelonephritis	5
Pre-eclamptic toxemia	2
Convulsive toxemia	2
Vomiting of pregnancy	4
Miscellaneous	2
	15
Total	49

Vomiting of Pregnancy. This group of four patients was observed between 1931 and 1933. It includes a thirty-one-year-old primigravida in whom uncontrolled vomiting developed at three and one-half months; a twenty-five-year-old primigravida in whom uncontrolled vomiting developed at four months; a thirty-four-year-old gravida five, with previous normal pregnancies in whom uncontrolled vomiting developed at four and one-half months and a twenty-two-year-old primigravida in whom severe vomiting

FIG. 5. A, Case III, a thirty-seven year old woman with bilateral symmetric renal cortical necrosis. Low power view showing infarctive necrosis of the renal cortex. There is extravasation of erythrocytes into the interstitial tissue but the outlines of cortical architecture are well preserved; hematoxylin and eosin, × 25. B, same case. Medium power view showing boundary between infarcted cortex and "spared zone." Hemorrhagic necrosis of a glomerulus and hemorrhage into a tubule are shown; hematoxylin and eosin, × 100. C, Case VII, a twenty-five year old woman with bilateral symmetric renal cortical necrosis. Low power view showing a branching thrombus in an interlobular artery and its subdivisions. The surrounding cortex shows coagulation necrosis; hematoxylin and eosin, × 30. D, same case. Detail showing thrombus extending along an afferent arteriole up to a glomerulus. The pattern of fibrin formation is from the side of the interlobular artery toward its center. There is no morphologic evidence of progressive retrograde thrombus formation; hematoxylin and eosin, × 90.

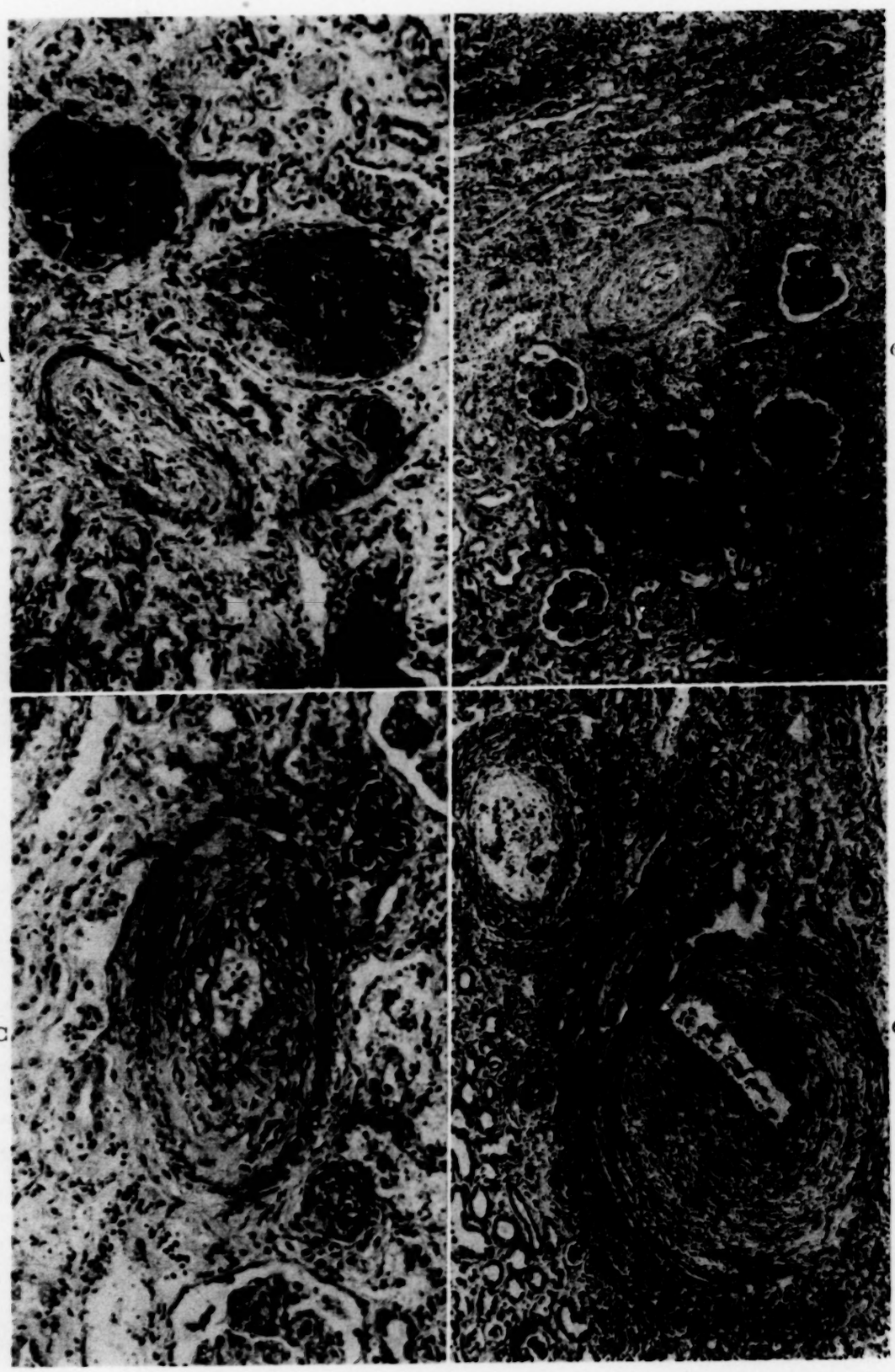


FIG. 6.

developed at eight months. None of these patients had hypertension at any time and only the last patient had albuminuria and a blood non-protein nitrogen which rose to 120 mg./100 ml. the day before death. Urinary output in all these patients was satisfactory and of no clinical concern. All these patients died before delivery. Autopsy in two instances disclosed a renal lesion labelled initially as "fatty degeneration of the tubular epithelium." Stains for fat disclosed only minimal traces of sudanophilic material within the large single vacuoles which distorted the cytoplasm of the tubular epithelial cells. The vacuolar change was patchy and inconstant. Where encountered it involved both proximal and distal convoluted segments of the tubule. There was no evident necrosis of tubular epithelium and, presumably, the lesions were reversible. In recent years tubular vacuolization has been described in patients with lowered serum potassium levels as a result of chronic diarrhea[9–12] and as a result of the administration of chelating agents.[13] Currently, this alteration of renal tubular epithelium is being labelled hypokalemic vacuolar nephropathy. (Fig. 3.) Mild focal fatty infiltration of the liver was observed in three of the patients with hyperemesis. As is usual in such cases, the anatomic observations at postmortem failed to disclose the cause of vomiting. However, in two cases the cause of death was pulmonary edema, in one case bronchopneumonia and in one case bilateral adrenal hemorrhages. Death usually occurred after vomiting had been controlled and while the patient was being treated with glucose and saline infusions. (Fig. 6D.)

The toxicity of sodium-containing solutions when administered to patients with severe potassium depletion has been previously emphasized.[14] The antagonism between sodium and potassium may aggravate the effects of potassium depletion with particular regard to the initiation of cardiac arrythmias. Digitalized patients are peculiarly susceptible in this regard. Even the administration of glucose which normally results in decrease in serum potassium levels may be dangerous in this situation.[15] In the light of current information, these patients may have died in electrolyte imbalance, possibly with low blood potassium levels.

Miscellaneous. Eight of the forty-nine fatal cases are listed in Table I under miscellaneous; of these, four had anuria, two had oliguria and two had no diminution of urine output. In these cases, the renal lesion was either secondary to a disease process elsewhere in the body or else not inherently related to the patient's pregnancy. For the sake of completeness, these cases are included and summarized in Table VIII.

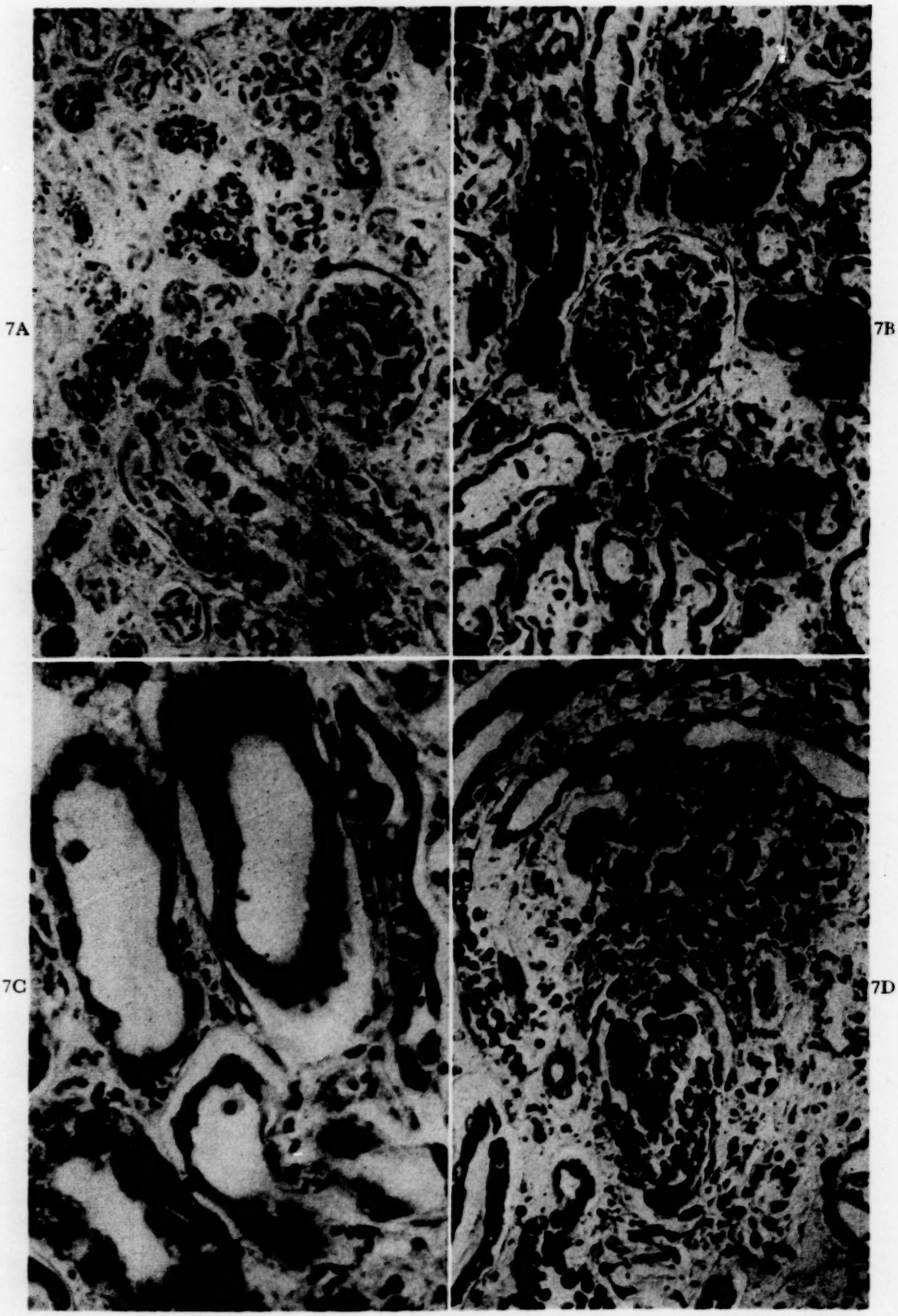
Of this group of eight miscellaneous cases, four patients had severe rheumatic heart disease and died of sepsis. In this group of cases the renal lesions appeared as one or another of the forms of hematogenous infection. In two patients the renal lesion must be considered iatrogenic (ligation of aberrant arteries, sensitivity reaction to drug therapy).

Non-Fatal Cases

Of the thirty-one patients who recovered and are included in this study, twenty-six were associated with anuria and five with oliguria as defined. A biopsy of the kidneys was not performed on any of these patients. Therefore it is not possible to prove histologically the character of the renal lesion in any individual case. When, however, the patient's clinical history is studied and compared to the clinical histories of patients who have died, it is possible to offer a valid bedside diagnosis of the type of renal lesion present. It follows that the management must be viewed against the etiologic background and natural history of the renal lesions.

Fourteen cases (45.1 per cent) were complicated by varying degrees of uterine hemorrhage. Five of these involved toxic premature separation of the placenta and two were cases of nontoxic separation. The remainder included seven

FIG. 6. A, Case III, a thirty-seven year old woman with bilateral symmetric renal cortical necrosis. Medium power view near the edge of an infarcted zone. One glomerulus shows hemorrhagic necrosis; the other shows coagulation necrosis. An arteriole shows segmental "smudgy" necrosis of its wall and contains a thrombus. An interlobular artery shows loose fibrous proliferation of its intima; hematoxylin and eosin, × 125. B, Case VI, a twenty-two year old woman with bilateral symmetric renal cortical necrosis. An interlobar artery at the margin of a zone of infarction shows fibrous proliferation of its intima. Part of the adjacent cortex is necrotic and there is hemorrhage into tubules; hematoxylin and eosin, × 75. C, same case. Detail showing almost complete obliteration of the arterial lumen by the proliferated collagenized intima. An adjacent small arterial branch shows edema of its wall and some medial proliferation; hematoxylin and eosin, × 200. D, Case V, a thirty-seven year old woman with bilateral symmetric renal cortical necrosis. Extensive fibrous intimal proliferation of an arcuate artery has reduced the lumen to a narrow slit. An adjacent interlobar artery shows moderate proliferation of its intima; hematoxylin and eosin, × 70.



7A 7B

7C 7D

FIG. 7.

cases of hemorrhagic shock involving uterine atony which occurred after completion of the third stage of labor; of these, hemorrhagic shock developed in five patients following cesarean section and in two following pelvic delivery. Table II reveals the distribution of the other

TABLE II
NON-FATAL CASES OF DEPRESSED RENAL FUNCTION

I. Patients with Anuria	
Hemoglobinuric nephrosis	9
(Incompatible blood – 8; water hemolysis – 1)	
Hemorrhagic shock, postcesarean	5
Hemorrhagic shock, postpartum	2
Abruptio placentae	7
(Toxic – 5: Non-toxic – 2)	
Toxemia with postpartum convulsions	2
Drug sensitivity (postabortal)	1
	26
II. Patients with Oliguria	
Mesenteric thrombosis, postcesarean	1
Sepsis, postpartum	2
Amniotic fluid embolism	1
Diabetic coma	1
	5
Total	31

cases comprising this group. It is a varied listing of isolated clinical entities, but from it emerges the observation that the feature common to all the cases in this group is an element of shock. This is true in the cases of hemoglobinuric nephrosis induced by water hemolysis or transfusion with incompatible blood; it is also present in severe cases of premature placental separation, post-abortal drug sensitization, amniotic fluid embolus, mesenteric thrombosis after cesarean section, and the like.

Incompatible blood transfusion accounted for 29 per cent of the cases with non-fatal complications of the kidneys. The hazards associated with blood replacement are common knowledge but must still be emphasized. Inasmuch as obstetrical hemorrhage has become the major factor in maternal mortality and morbidity, and generally involves an acute, profuse, unanticipated episode, the great need for planned management of

TABLE III
FATAL CASES OF ANURIA 1948 TO 1954

Renal cortical necrosis	2
Acute tubular necrosis	5
Convulsive toxemia	1
Miscellaneous*	2
	10

* Includes one case of necrotizing allergic arteritis and one case of malignant nephrosclerosis superimposed upon recurrent glomerulonephritis.

blood bank facilities in an obstetrical service is re-emphasized. It should include a working arrangement for prompt administration of adequate amounts of compatible blood.

Toxemia of pregnancy was encountered in seven cases (22.5 per cent) in this group. The impression gained from this study is that the reduction in renal function, related purely to toxemia of pregnancy, is not the result of widespread alteration of the renal paranchyma but rather extrarenal in origin, transient in nature and from which clinical and renal recovery is predictable, barring medical mismanagement or maladroit delivery. This favorable prognosis is altered, however, by the complications that occur in the toxemic patient, whether they are related to placental separation or to the mode of delivery. It is the element of shock superimposed upon the basic vascular alteration of toxemia which is the hazardous factor and it is against this factor preventative attention should be directed.

The nature of the management of purely obstetrical circumstances is of some interest. In

FIG. 7. A, Case II. Acute tubular necrosis, ischemic type. Medium power view showing necrosis and desquamation of tubular epithelium. There is no hemorrhage into the tubules nor heme cast formation. The patient died in anuria and shock forty-two hours after massive hemorrhage from placenta previa; hematoxylin and eosin, × 125. B, Case VII. Acute tubular necrosis, hemoglobuinuric type. Medium power view showing heme casts filling proximal convoluted tubules. B. welchii (Cl. perfringens) infection developed following a spontaneous septic abortion. Although the infection was controlled by antibiotics, the patient died fourteen days later in anuria and uremia despite dialysis; hematoxylin and eosin, × 125. C, acute tubular necrosis. Tubular regeneration is shown. One tubule is lined by low cuboidal epithelium. Another tubule shows syncytia of regenerating epithelial cells. A mitotic figure is seen in the epithelium of a well regenerated tubule. Intraacytoplasmic "hyaline droplets" are present in the tubule at the lower left; hematoxylin and eosin, × 300. D, acute tubular necrosis. A medullary granuloma has developed at the site of tubulorhexis. Many eosinophils are found among the infiltrating inflammatory exudate. Phloxine and methylene blue, × 250.

fourteen of the total of thirty-one patients, pregnancies were terminated by pelvic delivery, in thirteen by cesarean section and in two by dilatation and curettage. The remaining two involved a breech extraction and an incomplete manual removal of a hydatidiform mole *per vaginam*. Without exception, whether it be uterine atony after pelvic delivery, cesarean section or simply dilatation and curettage, excessive blood loss was the most vital clinical problem. While it is difficult to distinguish between cause and effect, the features shared by all these patients appear to be blood loss and resulting shock. At times, this was recognized early and blood replacement attempted. In some unfortunate instances, incompatible blood was used and a degree of additional shock added. Other instances involved a difficult, traumatic pelvic delivery or an episode of hypotension related to spinal anesthesia. Hysterectomy was resorted to in three patients in an attempt to control uterine hemorrhage.

Analysis of the fetal survival reveals that of a total of twenty-six viable infants, seventeen were liveborn while nine were stillborn, a salvage rate of 65.4 per cent.

The following three case histories are appended briefly to illustrate the nature of the clinical problem both in respect to the obstetrical circumstances and the ensuing disorders in renal function.

Case I. Mrs. R., a twenty-five year old gravida II, Para I, was electively scheduled for a repeat cesarean section following a normal uneventful pregnancy. The patient's only previous pregnancy had been terminated by a primary hysterotomy because of a persistent face presentation.

Under ether anesthesia a low cervical transperitoneal hysterotomy was performed. Five hundred cc. of whole blood was administered during the procedure, apparently a routine in this particular hospital for all cesarean sections. Unfortunately this proved to be an incompatible transfusion. On the first postoperative day the patient's total output consisted of 60 ml. of bloody urine. For the next six days the twenty-four-hour output never exceeded 40 ml. During this interim the serum non-protein nitrogen rose to 147 mg. per cent and the patient was intermittently drowsy and disoriented. On the seventh postoperative day, there being no evidence of improvement, the patient was transferred to the Peter Bent Brigham Hospital. Upon admission blood chemical studies revealed the following: blood urea nitrogen 134 mg./100 ml., CO_2 14.5 mEq./L.; serum chloride 87 mEq./L.; sodium 120 mEq./L. and potassium 6.3 mEq./L. The patient was watched carefully over the next several days inasmuch as the urinary output slowly improved and the chemical status was maintained. On the eleventh postoperative day, electrocardiograms revealed an abrupt development of hyperkalemic effects and the blood potassium was recorded at 8.4 mEq./L. Prompt dialysis was elected with an excellent clinical and chemical response. The blood urea nitrogen fell from 290 mg./100 ml. before dialysis to 90 mg./100 ml. afterwards. Other significant blood chemical alterations included CO_2 from 12.6 mEq./L. to 17.0 mEq./L., chlorides from 111 mEq./L. to 123 mEq./L. and the potassium from 8.4 mEq./L. to 4.4 mEq./L. On the following day the urinary output was 400 ml. and this improved rapidly thereafter. Interestingly, however, despite satisfactory chemical and renal response, the patient remained disoriented and difficult to manage until four days after dialysis. At this time sensorium dramatically cleared and the patient's recovery was uneventful and complete.

This case illustrates the hazards of incompatible blood transfusion in a normally pregnant patient. The inclination to abrupt potassium intoxication is to be noted. Dialysis after the onset of potassium intoxication affected prompt chemical correction, but clinical recovery was prolonged.

Case II. Mrs. C., a twenty-six year old, gravida IV (recently delivered), Para IV, presented a known history of hypertension with albuminuria and edema in a previous pregnancy, as well as a strong family history of hypertensive disease.

The present pregnancy was complicated throughout by an elevation of blood pressure which was recorded as high as 180 mm. Hg. systolic. With a low salt regimen, the patient's pregnancy progressed to the thirty-eighth gestational week at which time profuse vaginal bleeding developed, associated with lower abdominal pain, nausea and vomiting. Upon admission to the local hospital, the fetal heart tones were not audible. A diagnosis of abruptio placentae was made. Under spinal anesthesia the patient was treated by manual dilatation of the cervix followed by internal podalic version and extraction of a stillborn fetus. An element of uterine atony with hemorrhage was encountered but the history was vague regarding the amount of blood lost. The placenta was removed manually and the uterine cavity then was said to have been douched and packed. During these energetic procedures, 1,500 ml. of compatible blood was administered.

Following delivery absolute anuria developed. When this had persisted for five days the patient was transferred to the Peter Bent Brigham Hospital. On admission the significant blood chemical determinations were: blood urea nitrogen 76 mg./100 ml., CO_2 23 mEq./L., sodium 118 mEq./L., potassium 5.6 mEq./L. The patient was carefully observed during

the next week and it was anticipated that spontaneous diuresis with recovery would follow. However, on the twelfth postpartum day the patient complained of blurred vision and generalized paresthesias; the electrocardiogram showed peaking of T waves. Hemodialysis was therefore instituted with prompt return to a normal electrocardiogram pattern. Some six hours later the blood chemical determinations revealed the blood urea nitrogen 36 mg./100 ml. (previously 130), CO_2 27.5 mEq./L. (previously 19.5), chlorides 103.8 mEq./L. (previously 92.1), sodium 136 mEq./L. (previously 133), potassium 4.0 mEq./L. (previously 5.25). The following day the total urinary output was 325 ml. and it consistently improved; after the fourteenth postpartum day it remained normal with a peak to 1,400 ml. output on the twenty-second postpartum day. Since discharge, the patient has been seen on several occasions in follow-up visits and blood pressure appears stabilized at 190/130.

In the light of this study the clinical background strongly suggests that the basic kidney lesion was bilateral symmetrical cortical necrosis. The presence of antecedent hypertensive disease in a multiparous patient combined with severe placental separation forms the evidence for this opinion.

The obstetrical therapy employed is regarded as obsolete and the wonder is that the patient survived delivery to say nothing about the recovery from renal cortical necrosis. Regardless, this case illustrates the additional hazard of premature separation of the placenta in a patient with hypertensive disease and suggests the advisability of inducting labor in such patients whenever fetal viability is reached (thirty-fifth week) to prevent renal and other serious complications.

Case III. Mrs. J. A., a thirty-three-year-old gravida II, Para 0, had an uneventful prenatal course and entered a local community hospital in early labor. Her only previous pregnancy had terminated as a spontaneous abortion and the current pregnancy had occurred after a prolonged period of infertility.

After ten hours of desultory labor the patient was delivered of a viable infant by a transperitoneal low cervical cesarean section because of uterine inertia. Profuse hemorrhage from uterine atony occurred immediately postpartum. The patient received 2,000 ml. of compatible blood, but despite this therapy, deep shock was believed to have persisted for a minimum of two hours.

The immediate postoperative course was complicated by fever and drowsiness, with a total twenty-four hour urinary output of 5.0 ml. Fever and anuria persisted and on the third postpartum day the decision was made to transfer the patient to the Peter Bent Brigham Hospital. On admission, the laboratory findings included a marked proteinuria with many red and white cells as well as granular casts in the urinary sediment. The blood urea nitrogen was 84 mg./100 ml.; the blood CO_2 17.4 mEq./L.; serum chlorides 118 mEq./L.; serum blood sodium 142 mEq./L. and blood potassium 6.4 mEq./L.

By the fifth postpartum day the blood urea nitrogen rose to 185 mg./100 ml., the serum potassium to 8.0 mEq./L., while the serum CO_2, chloride and sodium had fallen to 15.8 mEq./L., 103.2 mEq./L. and 136 mEq./L. respectively. Clinically, the patient remained anuric while exhibiting a dull sensorium, general myasthenia and vomited continuously. On the fifth postpartum day, dialysis was accomplished with good chemical response. Some six hours after dialysis the blood urea nitrogen was 63 mg./100 ml., the CO_2 23.9 mEq./L., the serum sodium 142 mEq./L. and the serum potassium 4.9 mEq./L.

By the following day, however, total urinary output was but 100 ml. and the blood urea nitrogen had risen to 135 mg./100 ml. with accompanying changes in the total chemical picture. The serum potassium rose precipitously to 9.2 mEq./L. and was associated with definite electrocardiographic changes typical of potassium intoxication. A second dialysis was thus elected and within four and one-half hours the electrolyte and electrocardiographic picture reverted toward normal and the blood urea nitrogen was 52 mg./100 ml. The urinary output over the next four days improved gradually so that on the tenth postpartum day it measured 440 ml. On this day a third dialysis was completed with striking clearing of a clouded sensorium. By the eleventh postpartum day the urinary output was 605 ml. and thereafter a satisfactory diuresis ensued, reaching a peak on the seventeenth postpartum day with an output of 3,090 ml.

This case illustrates the hazards of hemorrhagic shock in an otherwise uncomplicated obstetrical situation. The importance of early recognition of potassium intoxication and the value of hemodialysis is evident. Without the latter, it is doubtful that the patient would have survived. The kidney lesion was presumably acute tubular necrosis.

COMMENTS AND SUMMARY

In large measure this study of fatal and nonfatal cases of acute renal complications of pregnancy was undertaken to relate our knowledge of clinical problems to pathologic problems. Pathologic study of the kidney in the patients who died furnishes a basis for classifying the nature of the lesions and provides an evaluation of their extent. Study of the clinical course in the patients who recovered, appraised in the light of clinical laboratory investigation, yields information that is essential for therapy. Within limits the necessary practical information is furnished by the answers to certain questions.

With respect to eclampsia, specific questions

were raised. Is depression of renal function in toxemia associated with any constant pathologic lesion? Is the depressed function intrarenal or extrarenal in origin? To what extent does impairment of renal function, although temporary, jeopardize the life of such patients? Do such lesions lead to irreversible damage of the kidneys and permanent alterations in their function?

Renal lesions attributed to toxemia were found in less than 50 per cent of the cases of unprovoked toxemia and these were restricted to the glomerular portion of the nephron. Glomerular lesions were not observed as frequently in our patients as they were in those reported by Bell[16] who noted these lesions in 51 of 52 patients with fatal eclampsia. In this respect our observations support those of Govan[17] who questioned the specificity of the glomerular lesion. Govan points out that comparable changes are found in the glomeruli of pregnant women dying from other causes without hypertension, albuminuria, edema or convulsions. He interprets the alterations in the basement membrane as indicative of a generalized endocrine effect on blood vessels during pregnancy. Sheehan,[18] in describing the renal changes associated with hypertensive toxemias, concludes that glomerular swelling to 1.5 times the normal mean is the most consistent lesion, but that thickening and reduplication of the glomerular basement membrane does not occur. It is rather that there is swelling of endothelial cells which lay down a fine network of fibrils beneath the basement membrane. These observations are consistent with the available physiologic data that renal blood flow is not decreased in toxemia of pregnancy but that the glomerular filtration rate may be significantly depressed.[19,20]

Tubular changes occur with some frequency according to Sheehan[18] but he regards "hyaline droplet" degeneration and the presence of an occasional cast as non-specific. "Hyaline droplets" in tubular cells may merely represent the resorption of protein (albumin) which has filtered through a slightly damaged glomerulus. Oliver[21] has shown that hyaline droplet degeneration is not a degenerative change but is evidence that the tubular epithelium is functioning fairly well. Allen,[22] however, cautions that hyaline droplets are not invariably equitable with tubular resorption of protein and may indicate metabolic alterations in tubular epithelial cells, although these alterations need not result in irreversible cell damage. Our observation of minor tubular changes in eleven of thirteen patients with fatal eclampsia confirms the general impression that there is no significant or characteristic tubular lesion in pregnancy toxemia.

In only two cases were necrotizing lesions of afferent arterioles present; these were similar to those found in hypertensive states in both non-pregnant women and in men. In his series, Govan[17] noted fibrous thickening and reduplication of the internal elastic membrane of the larger branches of the renal artery in 50 per cent of the cases. Eight of the sixteen patients with arterial lesions had a history of hypertension during previous pregnancies. Govan's observations are substantially in agreement with those made several years previously by Baird and Dunn.[23] It is of interest that both publications refer to the fact that efforts to identify a "toxin" in eclampsia have been unsuccessful and proceed to cite observations from experimental endocrinology which furnish suggestive evidence regarding the nature and development of the disease. Therefore, the occasional observation of necrotizing inflammation of the arterioles in an unprovoked eclampsia is better construed as an effect of the acute elevation of blood pressure. Similar lesions can be produced regularly in animals by acute hypertension experiments.

It seems likely that any depression of renal function in severe, unprovoked toxemia is transient and reversible unless some further complication is superimposed, such as premature separation of the placenta, postpartum hemorrhage or any other circumstance bearing with it an element of shock. Renal plasma flow is reduced in pregnancy toxemia when compared with the elevated values obtained during normal pregnancy.[19,20] The rate of renal plasma flow in pregnancy toxemia, however, is well within the range of values for normal non-pregnant women. This is in sharp contrast to a reduction in plasma flow in patients with acute tubular necrosis when determined forty-eight hours after the onset of the anuria.[1] On the basis of the meager demonstrable renal changes it must be concluded that any reduction in renal function in pregnancy toxemia is due primarily to extrarenal sources.

None of the women with convulsive toxemia in this study died in renal failure. At most, a limited degree of azotemia was present during the height of the toxemic episode. While many methods have been employed to improve renal function in eclamptic or pre-eclamptic women,

one wonders if it is necessary for the ultimate recovery of the patient. If the decreased urine output is extrarenal in origin, more effective diuresis might be accomplished by methods directed at the hormonal control of renal function. Most of the methods currently in use fall into two major groups; those aimed at increasing glomerular filtration and those designed to increase renal blood flow, despite the fact that in the latter group renal blood flow is not reduced to pathologic levels. No method has met with conspicuous success and it seems entirely possible that any therapy which may produce a significant hypotensive episode is potentially dangerous. The only toxemic cases encountered in this study associated with renal failure sufficient to jeopardize the patient's recovery were those in which medical or obstetrical mismanagement further compromised the patient's welfare. The actual cause of death in the majority of patients with severe toxemia was cerebral edema with or without cerebral hemorrhage and/or pulmonary edema. Certainly whatever is the cause of death in a patient with unprovoked severe toxemia, it apparently is not acute renal failure. Efforts directed solely toward improving renal function, therefore, are not a requisite in the treatment of the acute phase of pregnancy toxemia. Until more is known of the cause of edema in this disease, nothing short of termination of the pregnancy, presumably with the removal of the endocrine effects of the placenta, will restore renal function to normal.

In view of the unimpressive nature of the glomerular lesion in these cases, it is not surprising that whatever anuria or oliguria is present should be transient and reversible. However, the question arises whether or not a single episode of unprovoked severe toxemia, with or without convulsions, results in any permanent alteration of the renal structure. Many efforts have been made to answer this question. For example, among the more intensive studies McKelvey and MacMahon[24] studied thirteen patients who died of renal failure and who had had toxemia during a previous pregnancy. Six of these patients were colored women who had symptomatic hypertensive disease before the pregnancy in which toxemia developed; they died ultimately with malignant nephrosclerosis. The remaining seven patients were an assortment of cases in which toxemia was present and who died at or near term, delivered or undelivered. Postmortem examination of these women showed the acute lesions of eclampsia to a greater or lesser degree as well as a variety of other lesions associated with their terminal illnesses. In four of these cases there was microscopic evidence of renal disease of some duration prior to the gestation. It is clear that McKelvey and MacMahon were not dealing with cases of unprovoked eclampsia, but rather with patients who had underlying renal-vascular disease, who had become pregnant and in whom pre-eclampsia and eclampsia then developed. Although it is plausible to infer that pregnancy complicated by eclampsia may accelerate an underlying renal-vascular disease, these investigators furnish no evidence regarding the sequelae of unprovoked toxemia.

Likewise, Page and Cox[25] failed to show that unprovoked toxemia results in permanent damage to the function or structure of the kidneys. Their study is based upon twenty-six cases in which clinical and autopsy material was available. Of these, seven patients died of eclampsia and three died in the severe phase of pre-eclampsia. The remaining sixteen patients were divided into two groups—a group of six patients who had had toxemia during a pregnancy which terminated one to twelve years before their death, and a control series of ten patients uncomplicated by toxemia who died shortly after delivery. Although glomerular basemen membrane thickening was present in all six patients with antecedent toxemia, it was also present in five of the ten controls but not to such a severe degree. Renal tubular and vascular lesions were absent in all cases. One cannot, however, rule out the possibility that in the former group concurrent or intercurrent hypertensive disease had developed independent of the history of pregnancy complicated by toxemia.

The study of Corcoran and Page[26] indicates that renal function differs in cases of unprovoked toxemia from those in which there is a hypertensive background. They found that the filtration fraction was increased in cases of toxemia with pre-existing or latent hypertension but that it was decreased in cases with unprovoked toxemia, the latter finding being consistent with decreased filtration rate and normal renal blood flow. In the milder cases of both groups, however, there was no significant change in the filtration fraction. If, as is inherent in hypertensive disease, renal plasma flow is decreased, the filtration fraction will be increased. Therefore,

the analytical survey of data furnishes little basis for distinguishing between the effects on the glomerulus in unprovoked toxemia when contrasted with toxemia developing in a hypertensive patient. Corcoran and Page do point out that a in few patients who showed a decreased filtration rate during the acute course of toxemia an increased filtration fraction and arterial hypertension developed later.

A purely clinical study from a retrospective point of view was done by Teel and Reid[27] who reported on a follow-up study of eighty patients with severe convulsive toxemia. These investigators found that of twenty-nine posteclamptic patients who were known to be healthy and free of vascular or renal disease prior to eclampsia, none showed albuminuria or evidence of impaired renal function and only three showed hypertension. In a similar study[28] on the sequelae of non-convulsive toxemias, the same authors learned that only one of forty-seven severe pre-eclamptic patients had definite persistent hypertension or albuminuria. In both studies, they observed that in cases of provoked toxemia (those in which evidence of antecedent renal disease and/or hypertension was noted), albuminuria and elevation of blood pressure persisted after delivery in almost every case.

Subsequent studies by Chesley and his colleagues[29,30] have supported these observations. Chesley and Cosgrove followed up 262 of 270 women who survived an episode of acute eclampsia for one to twenty years. Of 181 white primiparous eclamptics there were five remote deaths, a mortality of 2.8 per cent; two of the deaths were due to cardiovascular-renal disease. In contrast, in a follow-up of 59 white multiparous eclamptic patients there were eight remote deaths, a mortality of 13.6 per cent; five of the deaths in this group were due to cardiovascular-renal disease. Although Chesley and Cosgrove had only twenty-four non-white patients in their series, a number too small for any definitive conclusions, the mortality was 23.5 per cent in previously primiparous colored women (four remote deaths in a follow-up of 17 patients) and 40 per cent in five multiparous colored patients (two remote deaths due to cardiovascular-renal disease). They attribute the increased mortality in the multiparous women to a higher incidence of hypertensive disease antecedent to the pregnancy which culminated in the eclampsia.

Chesley[30] summarizes the relationship of pregnancy toxemia to the kidney as follows: "So far as available information goes, it would seem that renal impairment does not underlie pre-eclampsia and eclampsia, although when renal impairment does exist there seems to be a predisposition to acute toxemia. Whether pre-eclampsia and eclampsia cause renal damage is an open question. Corcoran and Page, and Chesley have reported that pre-eclamptics with low filtration fractions are more likely to be left with permanent hypertension. The reduced filtration rate and filtration fraction in pre-eclampsia may be attributable to thickening of the basement membrane of the glomerular capillaries which has been described as typical of pre-eclampsia and eclampsia. Page and Cox found some evidence that this thickening persisted for months and years after toxemia. If the lowered filtration in pre-eclampsia be dependent upon such glomerular changes, and if the changes persist, then the post-toxemic hypertension could be a result of renal damage induced by the pre-eclampsia. However, the followed-up cases are very few, the glomerular lesion may be an artefact if the glomerular lesion does exist it may not persist, and it has not been proved that the lowered filtration fraction depends upon such a lesion. No renal function test has been developed which is of any value in assessing the severity and progression of pre-eclampsia."

It is difficult to believe that such inconspicuous, sparsely distributed lesions as encountered in the fatal cases of pregnancy toxemia in this study can result in permanent damage to a significant proportion of nephron units or to any permanent alteration in renal function. This adds support to the belief that patients who have normal blood pressure and renal function before the development of toxemia have little or no residual hypertension or abnormal urinary findings.

With respect to bilateral symmetrical cortical necrosis of the kidneys, the most important question is why do the majority of patients in whom abruptio placentae develops escape this devasttating lesion, and conversely, why are the few women in whom the lesion develops susceptible to it? Other questions suggest themselves. Do patients with this lesion recover? If so, is there a permanent alteration of renal function? What prognosis can be offered in a given case once the diagnosis is established? Does our understanding of the pathogenesis of the lesion offer any basis

for preventing its development or modifying its course? Reviews by Scriver and Oertel,[31] J. E. Ash,[32] Duff and Murray[33] and more recently Sheehan and Moore[34] and Burt and Kearns[35] have furnished considerable information regarding the nature and genesis of this lesion. Typical examples of the disease with clear-cut presentation of pathologic findings are readily accessible and well illustrated in articles by Sheldon and Hertig,[36] Gasper[37] and T. B. Mallory.[38]

A notable contribution to the pathogenesis of renal cortical necrosis was made by deNavasquez[39,40] who studied twelve cases of renal cortical necrosis; unfortunately, no individual protocols are presented. He was impressed by necrosis in the wall of the intralobular arteries which were thrombosed, and speculated that the medial necrosis was due to some circulating toxin which acted specifically upon the media of these vessels, producing paralysis of their walls, stasis within their lumina and conglutination of red cells without fibrin deposition. deNavasquez noted specifically that in none of his cases was there any evidence of a pre-existing vascular lesion in the major vessels of the kidney. (no arteriosclerotic change). Subsequently, he was able to produce similar lesions in rabbits' kidneys by injecting a staphylococcal toxin. In these animals he could find no evidence of vasopsasm whatsoever. Although Herzog,[41] Schuppel[42] and Glynn and Briggs[43] had advanced the idea that the thrombosis begins at the level of the afferent arteriole and is propagated in a retrograde direction along the arterial tree to the level of the interlobular arteries, deNavasquez pointed out that with paralysis of a segment of the arterial tree, prolonged stasis could lead to conglutination in the affected area which would be uniform and approximately simultaneous. Gaspar[37] also emphasized the role of bacterial toxins in the production of the lesion. A recent investigation by Thal[44] supports deNavasquez's observation that bilateral renal cortical necrosis can be produced in experimental animals by injection of staphylococcal toxin. By the use of an India ink perfusion technic, Thal was able to observe directly severe spasm of the renal vein and loss of pulsation in the renal artery. These changes developed within minutes after the injection of toxin and changes persisted for sufficient periods for bilateral necrosis to develop. Furthermore, Hedinger and Langeman,[45] while investigating the endocrine properties of carcinoid tumors found that metastatic tumors contain serotonin (5-oxy-tryptamin); repeated injection of 5-oxy-tryptamin into rats produced focal necrosis in the renal cortex similar to the lesions seen in humans as well as an increase in the platelet count in the peripheral blood.[45,46]

The case reported by Mallory occurred after a spontaneous abortion without sepsis; in this case pitressin was used to facilitate expulsion of the products of conception. Byrom[47] has reported on the experimental production of renal cortical necrosis by means of injection of pituitary extracts. Presumably, these lesions are the consequence of vasopressor action.

Duff and Murray[33] discuss the distribution of vascular thromboses, pointing out that they are confined to the interlobular arteries and the small arteries and arterioles that branch from them. They also demonstrate that there is considerable variation in the nature of the thrombotic material, some authors describe classical thrombi composed of platelets and fibrin enmeshing red and white blood cells, others describe homogeneous acidophilic masses, while still others describe the material occluding blood vessels as being composed of packed conglutinated red blood cells with little or no fibrin formation or platelet deposition. However, these investigators emphasize that irrespective of the nature of the occluding material the distribution in reported cases is the same, extending from the interlobular arteries along intralobular arteries into afferent arterioles and even into glomerular capillaries. Duff and Murray subscribe to the theory that prolonged and intense vasospasm may be responsible for the development of cortical necrosis, but they qualify this statement by saying "this mechanism is not necessarily the one responsible for the renal necrosis in all, or indeed any, of the cases of the disease." They state further, "any mechanism capable of causing more or less simultaneous and prolonged interruption of blood flow through a large number of the cortical arteries will produce the picture of symmetrical necrosis of the renal cortex. While the actual mechanism of occlusion, as it expresses itself in the final histologic picture in the cortical arteries and arterioles, appears clearly to be somewhat variable, it seems reasonable to suppose that certain factors in the etiology and pathogenesis of the vascular lesions are common to all cases." In implicating an etiologic agent, Duff and Murray speak of hypersensitivity or hyperirritability of the renal arteries, pointing out that alterations in the

TABLE IV

CLINICAL FINDINGS IN SEVEN CASES OF BILATERAL CORTICAL NECROSIS

Case	Age	Gravidity	History of Established Hypertension	Prenatal Course	Obstetrical Complication	Week of Gestation	Delivery	Condition Fetus	Blood Pressure	Urine Output (24 hr.)	Blood Nonprotein Nitrogen (mg. %)	Day of Death (postpartum)	Comment
I.	33	5	Unknown	Toxemia	Abruptio	33	Pelvic	Stillborn	200/100	Total anuria	115	7	Died in uremia
II.	40	4	Unknown	Toxemia	Abruptio	32	Pelvic	Stillborn	210/110	±12.0 ml	155	11	Convulsive seizure 4th day postpartum; died in uremia
III.	37	13	Unknown	Toxemia	Abruptio	26	Pelvic	Stillborn	220/120	±15.0 ml	225	8	Died in uremia
IV.	32	5	Unknown	Toxemia	Abruptio	31	Pelvic	Stillborn	198/128	±120 ml	...	2	Unsuccessful dialysis transperitoneal; patient never recovered from intrapartum shock
V.	37	2	Hypertension	Toxemia	Abruptio	35	Cesarean section	Neonatal death	190/140	Total anuria	143	11	Couvelaire uterus; postoperative shock
VI.	22	4	Hypertension	Toxemia	Abruptio	29	Pelvic	Stillborn	176/100	±100 ml	100	16	Unsuccessful hemodialysis (13th and 15th postpartum days)
VII.	25	3	Negative	Toxemia	Abruptio	29	Pelvic	Stillborn	150/90	±210 ml	97	15	Unsuccessful hemodialysis, 12th postpartum day

blood which might favor intravascular clotting must be of secondary importance in view of the fact that the thromboses are so sharply restricted to the kidneys and, in fact, to one particular segment of the kidney vessels. They conceive a hypothetical sequence of events which they characterize as a "series of vascular disturbances of increasing severity: intense vasospasm; vasoparalysis; partial or complete necrosis of the arterial walls which might be due either to vascular spasm of extreme intensity or the direct action of some toxic substance."

In effect, the point of view which Duff and Murray so ably champion is substantially the point of view held by most writers since 1941. Two recent symposia,[48,49] mostly concerned with the specific physiology of the renal circulation and whether or not the vasospasm is initiated by neural or humoral mechanisms, add but little to concepts of pathogenesis. Sheehan and Moore[34] apparently concur in the idea of vasospasm, coining a term "operative spasm" to indicate a spasm which results in observable ischemic lesions. This is a fortunate term, for one of the limits of the methods of morbid anatomy is that vascular spasm is not seen as such in postmortem tissues, and the pathologist can only see spasm by its results. In this respect, pathologic methods are more fruitful in cases of renal cortical necrosis than in eclampsia where the spasm, if present, is not so intense and is certainly transient and reversible. Thal's[44] direct observations of renal vascular spasm support the above hypotheses. It is of some interest that Thal observed that the vasospasm which ensued following injection of staphylococcal toxin was restricted to the kidneys and that the other intra- and retroperitoneal vessels were not involved.

The monograph by Sheehan and Moore[34] establishes unequivocally the histopathologic nature of renal cortical necrosis. There is no remaining doubt that the necrosis is secondary to thrombosis of segments of the renal vascular tree, that it is a true infarctive coagulation necrosis. Sheehan and Moore classify the lesion on the basis of its extent and divide it into four groups: focal, minor, patchy and gross. The anatomic extent of the necrosis depends entirely upon the number and distribution of intra-arterial thromboses and the amount of renal tissue so destroyed determines whether the patient recovers or dies. In this respect, it is of importance to observe that

TABLE V

AUTOPSY FINDINGS IN SEVEN CASES OF BILATERAL CORTICAL NECROSIS

Case	Age	Gravidity	Kidney Findings				Other	Photomicrograph
			Weight	Gross	Microscopic	Vessels		
I.	33	5	285 Gm. (each)	Extensive bilateral symmetrical cortical necrosis	Coagulation cortical (a) necrosis (b)	Sclerosis of intralobular arteries, afferent arterioles	Ischemic necrosis anterior pituitary	Figure 4
II.	40	4	R-214 Gm. L-200 Gm.	Extensive streaky hemorrhagic cortical necrosis	Necrosis with thromboses intralobular arteries	Renal arteriosclerosis; thickened intima, arcuate and interlobular arteries	Focal necrosis liver and pituitary	Figure 3D
III.	37	13	240 Gm. (each)	Mottled cortex, hemorrhagic necrosis	Cortical necrosis with glomerular hemorrhage	Fibrous proliferation of intima of interlobular arteries	Diffuse thrombosis of arterial tree	Figures 5A and B Figure 6A
IV.	32	5	180 Gm. (each)	Mottled cortex, hemorrhagic necrosis	Extensive coagulation; necrosis of glomeruli and tubules	Moderate internal thickening of interlobular and arcuate arteries	Hemorrhagic coagulation necrosis of liver	Figure 3C
V.	37	2	R-190 Gm. L-180 Gm.	Mottled punctate cortical necrosis	Diffused hemorrhagic necrosis	Diffuse, concentric endothelial proliferation of interlobar arteries, less in interlobular arteries	Diffuse renal vascular thrombosis	Figure 6D Figure 3A
VI.	22	4	200 Gm. (each)	Generalized necrosis with punctate hemorrhage	Diffuse cortical necrosis; about 20% "spared"	Moderate sclerosis of interlobular and arcuate arteries	Extensive thrombosis of interlobular arteries	Figures 6B and C
VII.	25	3	R-230 Gm. L-200 Gm.	Cortical necrosis with petechial hemorrhages, extensive	Extensive coagulation; necrosis	Intimal thickening and fibrosis of moderate degree in interlobar arteries, less frequently in arcuate arteries	Extensive thrombosis of small vascular branches; ischemic necrosis of pituitary	Figures 5C and D

whereas Sheehan and Moore studied uteroplacental apoplexy in seventy-two cases, most of the patients died of causes other than their renal lesions, with death occurring within twenty-four to seventy-two hours of their obstetrical accident. Most of the patients who succumbed within the first seventy-two hours died of severe shock, usually the result of massive hemorrhage. Sheehan describes at least thirty-three of these patients who had "lesions less severe than cortical necrosis," inferring that in these cases there was no time for cortical necrosis to develop. While these findings are analogous to one of our cases in which true cortical necrosis was present in a woman dying forty hours after uteroplacental apoplexy, (Table IV) the sudden death in this patient was due to potassium intoxication secondary to massive necrosis of the liver. Although cortical necrosis had developed before forty hours and anuria was present, sufficient time had not elapsed for uremia to occur. It is important to distinguish this type of case from the above group of cases described by Sheehan and Moore where the anatomic lesions were almost entirely confined to the tubules. We interpret these as cases of acute tubular necrosis (or less) rather than bilateral cortical necrosis, for in none of these was infarctive coagulation necrosis evident. *Rather, cortical necrosis in contradistinction to acute tubular necrosis develops early in the course of abruptio placentae and not merely as a consequence of a hypotensive episode. Our belief that the development of the renal lesion is acute and not progressive has important clinical connotations.*

In only twenty-three cases did Sheehan and Moore find renal cortical necrosis, as we understand the term, at postmortem examination. Of these cases, three showed focal lesions, three minor lesions, eight patchy lesions and nine gross lesions. Presumably, the renal lesion was only incidental to the cause of death in the six patients who had focal or minor necroses. Of the seventeen cases with patchy or gross variations, three patients died shortly after delivery. These were anuric, but the full clinical picture of uremia had not had time to develop. Ergo, out of the seventy-two cases in which Sheehan and Moore found areas of necrosis in the renal cortex, only fourteen (19 per cent) showed the full clinical and pathologic picture. This suggests clearly that there is a quantitative spectrum not only of the anatomic findings at postmortem but of the clinical picture. It is not an unwarrantable inference that of the patients, in whom abruptio

TABLE VI

SUMMARY CLINICAL FINDINGS IN NINE CASES OF ACUTE TUBULAR NECROSIS

Case	Age	Gravidity	Prenatal Course	Obstetrical Complication	Week of Gestation	Hemorrhage	Shock	Delivery	Condition Fetus	Urine Output (24 hr.)	Blood Nonprotein Nitrogen (mg. %)	Day of Death (postpartum	Remarks
I.	38	5	Normal	Non-toxic placental separation	39	++++	++++	Pelvic	Stillborn	± 150 ml.	...	2	Superimposed B. welchii infection
II.	35	5	Normal	Placenta praevia	38	++++	++++	Cesarean section followed by a hysterectomy	Alive	± 180 ml.	...	2	Never recovered from shock
III.	29	2	Normal	Volvulus large bowel	37	0	++++	Pelvic	Stillborn	± 150 ml.	153	3	Never recovered from shock
IV.	24	1	Normal	Criminal abortion	16	++++	++++	Dilatation and curettage	Nonviable	50 ml.	141	8	Hemodialysis performed twice
V.	31	2	Normal	Placenta praevia	30	++++	++++	Cesarean section	Viable	75 ml.	...	7	Incompatible transfusion
VI.	38	1	Toxemia	Toxemic intrauterine death	34	++	++++	Traumatic pelvic delivery	Stillborn	± 180 ml.	276	15	Old cirrhosis, satisfactory hemodialysis; incompatible blood transfusion
VII.	35	8	Normal	B. welchii septicemia with premature labor	22	0	±	Pelvic	Stillborn	± 100 ml.	277	14	Potassium intoxication; hemodialysis; retained placental fragments
VIII.	27	2	Normal	Post cesarean hemorrhage; hemorrhagic diathesis	39	++++	++++	Elective repeat cesarean section	Viable	90 ml.	173	10	Incompatible blood; potassium intoxication; unsuccessful dialysis
IX.	21	3	Normal	Inversion of uterus	40	++	++++	Pelvic followed by laparotomy	Viable	200 ml.	94	8	Overhydration; pulmonary edema; prolonged shock

placentae develops in the course of severe toxemia of pregnancy, those with severe oliguria or temporary anuria may indeed have focal or minor areas of cortical necrosis, but because the quantity of renal tissue destroyed is small, they recover following treatment. Of Sheehan and Moore's seventy-two cases, fourteen exhibited the usual picture, nine the same picture but to a lesser degree with death due to other factors, and forty-nine furnished collateral evidence which bears upon the pathogenesis of the lesion.

Analysis of the kidneys in the seven fatal cases in this study reveals that in every case there was a degree of *renal arteriosclerosis* usually in the arcuate and interlobar arteries, and that the thrombi which produced the infarctive coagulation necrosis lay distal to the sclerotic vessels. The degree of arteriosclerosis was pronounced in the older women in this group, those between thirty and forty years, and although less marked in the younger women, was noticeable. Review of the literature indicates that other observers have sporadically noted the presence of antecedent nephrosclerosis in cases of cortical necrosis, but have failed to assign it any particular pathogenetic significance. The present study, however, suggests that the pathogenesis of bilateral cortical necrosis involves renal arteriosclerosis. The inference is that the presence of nephrosclerosis increases the vulnerability of the kidney to the insult of abruptio placentae and the vast majority of women with the latter complication whose kidneys escape this lesion presumably have

TABLE VII

SUMMARY AUTOPSY FINDINGS IN CASES OF ACUTE TUBULAR NECROSIS

Case	Age	Obstetrical Complication	Day of Death	Kidney Findings	Other Findings	Miscellaneous
I.	38	Non-toxic placental separation	2	Tubular necrosis with heme casts	Generalized B. welchii lesions of liver and uterus	Massive shock
II.	35	Placenta praevia	2	Diffuse, ischemic necrosis of almost entire tubular epithelium	Pulmonary edema	Figure 7A
III.	29	Volvulus large bowel	3	Ischemic necrosis of tubular epithelium	Gangrene; perforation and early peritonitis	Overwhelming shock
IV.	24	Criminal abortion	8	Acute, tubular necrosis heme casts	Perforation of uterus with peritonitis; bilateral adrenal hemorrhages	
V.	31	Placenta praevia	7	Hemoglobinuric nephrosis	Venous mesenteric thrombosis of small bowel	Hemorrhagic diathesis secondary to imcompatible transfusion
VI.	38	Toxemic intrauterine death	15	Acute tubular necrosis with regeneration	Old portal cirrhosis with some acute damage necrosis; anterior pituitary	Figure 7C
VII.	35	B. welchii septicemia	14	Hemoglobinuric nephrosis secondary to Cl. perfringens hemolysis	Retained placenta with Cl. perfringens infections	Figure 7B
VIII.	27	Postcesarean hemorrhage	10	Acute tubular necrosis	Central necrosis of liver; retroperitoneal hematoma compressing sigmoid and right ureter	Consistent with prolonged shock and anoxia
IX.	21	Inversion of uterus	8	Healing stage of tubular necrosis, tubulorrnexis	Pulmonary edema	Figure 7D; cause of death, pulmonary edema

essentially normal renal blood vessels. Whether or not this is a chance observation, it indicates the need for further anatomic studies and certainly has significance in the prognosis for patients who enter pregnancy with hypertensive disease. Moreover, it adds another etiologic factor to be considered in the pathogenesis of the condition, and is compatible with the clinical observation that over 65 per cent of the reported cases of renal cortical necrosis complicating pregnancy occur in multiparous women over thirty years of age when hypertension begins to appear with greater frequency.

The prognosis in any individual case in which a diagnosis of renal cortical necrosis is made is grave, but review of the literature indicates that there are a few well documented cases of renal cortical necrosis which have recovered.* In these cases the necrosis was focal, for recovery is a function of the amount of kidney tissue spared. It is quite probable that less severe, non-fatal cases of renal cortical necrosis occur following abruptio placentae in which the correct diagnosis of the renal lesion is not made in the absence of histopathologic evidence. The frequency with which recovery occurs and the extent of permanent functional damage cannot be estimated as yet. The answer will depend on obtaining biopsy specimens of the kidney from patients who survive acute renal failure complicating pregnancy.

Although we are unable to define the nature of the renal insult, its mode of action appears to be one of prolonged intense renal vasospasm, probably affecting both arterial and venous channels. Following the spasm, there is a period of vascular paralysis in which blood flow is reduced and thrombi form. It has not been determined whether anoxic damage to vascular endothelium occurs during the period of intense spasm. If so, this would further favor the precipitation of

* See Footnote, page 787.

TABLE VIII

CLINICAL AND AUTOPSY FINDINGS OF MISCELLANEOUS GROUP

Case	Age	Gravidity	Past History	Prenatal Course	Complication	Week of Gestation	Urinary Output (24 hr.)	Day of Death	Autopsy Findings	
									Kidney	Other
					I. *Anuric Group*					
I.	31	1	Rheumatic heart disease	Normal	Acute bacterial endocarditis	40	90 ml.	4	Focal, embolic glomerulonephritis; renal infarcts	Septic infarcts lungs and spleen
II.	29	1	Glomerulonephritis	Normal	Postpartum (3 wk.) anuria	Postpartum 21 days	Anuria	21	Subacute glomerulonephritis; diffuse vasculitis	
III.	29	5	Negative	Hyperemesis gravidarum	Premature labor; intrauterine death	16	Total anuria	1	Fibrin thrombus; formation in glomeruli	Fatty metamorphosis of liver
IV.	20	1	Negative	Normal	Thrombocytopenic purpura	40	Anuria	70	Healed tubular nephrosis	Necrotizing allergic arteritis; related to drug therapy
					II. *Oliguric Group*					
V.	22	1	Rheumatic heart disease	Satisfactory	Pyelitis, acute	34	±120 ml.	7	Pyelonephritis, mild	Mitral stenosis
VI.	26	3	Negative	Nephrolithiasis	Nephrostomy and peritonitis	29	±200 ml.	6	Renal infarction secondary to ligation of aberrant artery	Diffuse peritonitis acute ulcer, cecum
					III. *Normal Output Group*					
VII.	31	1	Rheumatic heart disease	Cardiac difficulties	Pelvic peritonitis secondary to cesarean section	38	Normal	6	Septic renal infarcts	Generalized peritonitis
VIII.	36	1	Rheumatic heart disease	Septicemia	Acute bacterial endocarditis	29	Normal	28	Septic renal infarction	Acute bacterial endocarditis; septic infarction of spleen

fibrin from serum and the conglutination of erythrocytes and platelets. Once the thrombi are formed coagulation necrosis of the cortex (all structural elements distal to the thrombi) is inevitable. Usually there is a failure of urine formation within an hour or two after the acute onset of placental separation; presumably the interval between abruption and infarction is relatively short. The observation that the thrombi appear to be uniform in age and structure in any individual case affords no support for theories which postulate spasm restricted to the afferent arterioles with thrombin formation at that level and retrograde propogation. Apparently the thrombi form all at once over a short span of time. In all probability, by the time a patient with uteroplacental apoplexy is admitted to the hospital, whatever damage there will be to the kidneys has already been determined and there is little further damage unless mismanagement compromises them. There is no evidence to suggest a progressive lesion with implications of further renal impairment if recovery occurs.

Under these circumstances, treatment should be prompt, carefully applied, and hopeful, although the salvage rate is low. It is difficult to distinguish at the onset of the disease the few patients with focal or minor necroses who may recover from those with confluent or gross necroses who will die. It is best to assume that whatever degree of shock is present is due to combined external and concealed hemorrhage and restoration of blood volume is indicated. Termination of the pregnancy can be delayed until a propitious moment. Little is to be gained by a hasty hysterotomy on a patient in precarious condition. This only adds to the total amount of shock and invites further damage to the kidneys. The possible complication of hypofibrinogenemia should be considered and measures instituted promptly to diagnose and treat it.[50]

In general, prevention of renal cortical necrosis

is preferable to treating it. The increased risk of pregnant woman with antecedent hypertension to placental separation demands careful medical supervision of their vascular disease and a consideration of obstetrical intervention for early delivery, compatible with fetal viability. Such a program should not only minimize the risk of abruptio placentae and subsequent cortical necrosis but also decrease intrauterine fetal loss from superimposed pregnancy toxemia.

With respect to acute tubular necrosis, the principal questions are those of preventability, management and residual functional renal damage. This syndrome is not peculiar to pregnancy and what has been written, notably by Bull,[1] Oliver[7] and Swan and Merrill,[51] is applicable to these cases. In contrast to the non-obstetrical patient, the preventable affect of this syndrome is worthy of emphasis with respect to the pregnant patient and, if properly managed, the majority of these should recover. This is in contrast to Lucké's[6] original estimate that the "mortality in lower nephron nephrosis is 90 per cent—although not related to the ability of the tubular cells to regenerate but rather a failure of the patient to survive sufficiently long for renal function to recover." Clinically, almost every case of acute tubular necrosis complicating pregnancy was the direct result of shock either from acute blood loss or a hemolytic episode. In those cases in which the hemorrhage was external, the tubular necrosis was ischemic. Where there was intravascular hemolysis, the acute tubular necrosis was hemoglobinuric.

The most common cause of acute tubular necrosis in this study was intravascular hemolysis due to a transfusion of incompatible blood. Such errors occur when emergencies arise and personnel are under pressure. They are always preventable in retrospect. Another cause of acute tubular necrosis was hemorrhagic shock, the severity of which was misjudged and which was treated with insufficient blood replacement, usually after a period of delay. In a few cases hemorrhagic shock was the direct sequel of an ill-advised traumatic obstetrical maneuver. In other circumstances hemorrhagic shock complicated criminal abortions with and without sepsis. The pathologic physiology of hemorrhagic shock is no different in obstetrical patients than in surgical or non-surgical patients; the clinical aspects of importance are the unpredictability of its occurrence and the fact that blood loss is all too frequently underestimated. Although in many of these patients toxemia was a prominent feature, often sufficiently severe to serve as the indication for obstetrical intervention, renal failure was the result of shock during and after delivery. *It must be reemphasized that in this group one must avoid ascribing residual deficits in renal function to the effects of toxemia.*

Follow-up studies have shown that following recovery from acute renal failure there may be some diminution of renal function which is usually subclinical and not associated with nitrogen retention. More important, with respect to pregnancy is the fact that progressive diminution of renal function does not occur following recovery unless some other disease process causes additional damage to the kidneys. Such patients do not appear to be more susceptible to subsequent renal injury than do normals and, therefore, it is our feeling that in the absence of more than minimal impairment of renal function subsequent pregnancy is not contraindicated merely because of a history of previous acute tubular necrosis.

When a clinician is confronted with a patient in whom urinary suppression has occurred following abruptio placentae or severe toxemia, it can be of considerable importance to differentiate between acute tubular necrosis and renal cortical necrosis. In general, renal cortical necrosis is found in multiparous women over thirty years of age with established hypertension and with extensive premature separation of the placenta. Whereas acute tubular necrosis occurs in women of any age or parity who have any obstetrical complication sufficient to cause sustained renal ischemia as a result of shock. Consequently the amount and circumstances of the hemorrhage and the degree and duration of shock can be extremely helpful. Of particular importance, if obtainable, is the sequence of clinical events. If anuria is present before shock develops or is coincident with the early stage of vascular collapse, the diagnosis of renal cortical necrosis is more probable. Conversely, if shock exists over a period of time and then is followed by a reduction of urinary output to oliguric or anuric levels, the diagnosis of acute tubular necrosis is more likely. Obviously if any hemolytic element is present, such as transfusion reaction to a mismatched blood, the kidney lesion is acute tubular necrosis. Estimation of urinary volume and analysis of formed elements is of no special value in the differential diagnosis. Needle biopsy of the kidney can definitely distinguish the two

types of lesions but the procedure is not without risk. The importance of the correct diagnosis, however, lies not so much in the immediate treatment but rather in the ultimate prognosis which is very grave in renal cortical necrosis but more encouraging in acute tubular necrosis.

In recent years the importance of chronic pyelonephritis in relation to hypertension has been appreciated. In a goodly proportion of these cases the disease originates in the course of pregnancy. Too frequently, proper follow-up examination is not carried out for in a number of these patients the kidney infections tends to smolder quietly and without symptoms. In this era of specialization, such patients may seek or receive little medical supervision until they appear on medical services in their late 40's with hypertensive disease and badly damaged kidneys. Crabtree and Reid[54] have described the prevalence of this sequence of events.

The treatment of women with acute renal failure in connection with pregnancy is especially rewarding because they are young individuals, the majority of whom are in good health. Analysis of pathologic material in this study confirms the conclusions of other observers,[1,7] namely that tubular epithelium begins to regenerate within two to three weeks. If the patient can be sustained over this critical period of renal failure, the recovery of renal function is likely. In the interim careful attention to water and electrolyte balance, prevention of pulmonary edema, reduction of protein catabolism, replacement of excessive electrolyte losses during the diuretic phase are all important factors in the therapeutic regimen. These principles of therapy are now well established. The use of hemodialysis in the treatment of acute renal failure from whatever source should be considered when good conservative medical therapy has failed to control the progress of symptoms and signs which are due to uremia. Under these circumstances, it may be thought of as an adjunct to, rather than a substitute for, conservative management. In this sense its use should not be delayed until the patient is critically ill but transfer should be arranged to a center where dialysis is available under the coordinated efforts of the physician charged with the care of the patient and the operators of the artificial kidney. The onset of the clinical syndrome of acute spontaneous potassium intoxication is a particular hazard in the postpartum anuric patients.[55] Frequent electrocardiograms must be taken in such instances beginning with the fourth postpartum day. Where there is evidence of the progression of this syndrome the use of hemodialysis may be a matter of some urgency since this lethal complication responds well to this form of treatment when other methods fail.

Dialysis may be delayed in the face of oliguria or anuria if the clinical picture of uremia does not develop, for the organism can adapt to azotemia and acidosis within limits. If the usual "medical regimen" fails, however, the products of nitrogen metabolism must be cleared, the pH of the blood must be stabilized, and the optimal concentration of electrolytes secured lest irreversible damage to the heart or central nervous system be sustained.

CONCLUSIONS

1. Pregnant women comprise a greater proportion of patients in whom acute renal failure develops than is generally appreciated.

2. Analysis of the patient's clinical history and the circumstances preceding the development of anuria will usually permit the physician to furnish a diagnosis of the renal lesion present and to offer a prognosis.

3. The majority of patients in whom acute renal failure develops and complicates pregnancy suffer from acute tubular necrosis. This is usually the result of shock, either due to uterine hemorrhage or intravascular hemolysis. In large measure, this renal condition is preventable and, when it occurs, is manageable. The mortality approaches 25 per cent even with modern methods of treatment. Whatever renal damage may occur it is not chronically progressive. The question of future pregnancies will depend on the extent of initial damage sustained.

4. Renal cortical necrosis is an infrequent complication of severe abruptio placentae. It occurs chiefly in multiparous women over thirty years old. In this series, moderate to severe renal arteriosclerosis was present in all cases. It is inferred that nephrosclerosis increases the vulnerability of the kidney to infarctive coagulation necrosis which develops secondary to thrombosis of the renal arterial tree. Although recovery is possible, the prognosis is grave and some residual impairment of renal function seems likely.

5. The hazard of pyelonephritis complicating pregnancy is re-emphasized in terms of immediate risk, its chronicity and relationship to the subsequent development of hypertensive vascular disease.

6. Renal lesions in fatal cases of hyperemesis gravidarum may simulate those described as the result of potassium depletion. In retrospect, deaths from hyperemesis gravidarum which were considered to be "nutritional" could in some instances have been due to respiratory failure resulting from severe hypokalemia.

7. The renal lesion of severe toxemia of pregnancy is histologically inconstant, infrequent and inconspicuous. Although it is often associated with reduced urine output, the oliguria must be regarded as extrarenal in origin and must not be associated with significant renal damage unless medical or obstetrical complication intervenes in the form of shock or of a hemolytic episode.

8. An attempt to assess the permanent effect of severe pregnancy toxemia on the kidney indicates that the most important factors are the presence or absence of antecedent hypertensive-vascular disease and the occurrence of abnormal circumstances in delivery, more specifically, the presence or absence of a hypotensive episode.

9. In pregnant and postpartum women potassium intoxication may develop early in the course of acute renal failure. Therefore, in addition to accepted medical treatment, hemodialysis with the artificial kidney must be considered as a method of managing such patients early in the course of the disease.

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Case Reports

Extreme Obesity Associated with Alveolar Hypoventilation—A Pickwickian Syndrome*

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The purpose of this article is to consider the association of obesity, somnolence, polycythemia and excessive appetite. A careful study of one patient will be used to illustrate the discussion.

Review of Literature

The association of these characteristics has long been recognized. Medical texts of the early nineteenth century accept the association of these signs and symptoms as well established. The following quotation from Wadd[1] is an example. "A country tradesman aged about thirty, of a short stature and naturally of a fresh, sanguine complexion and very fat applied to me for assistance. He complained of perpetual drowsiness and inactivity. His countenance was almost livid and such a degree of somnolency attended him that he could scarce keep awake whilst he described his situation. In other respects he was well."

A classic description of the association of signs and symptoms under discussion was written by Charles Dickens.[2] The author refers to "A fat and red-faced boy in a state of somnolency." This boy was subsequently addressed as "Young Dropsy," "Young Opium-Eater" and "Young Boa Constrictor"—no doubt in reference to his obesity, his somnolence and his excessive appetite, respectively. A characteristic of these patients is an extraordinary degree of somnolence in which sleep may overcome the patient while he is sitting up or even while he is engaged in conversation or other muscular activity. The somnolence of his character was described by Mr. Dickens in the following words:

"A most violent and startling knocking was heard at the door; it was not an ordinary double knock, but a constant and uninterrupted succession of the loudest single raps, as if the knocker were endowed with the perpetual motion, or the person outside had forgotten to leave off.

"Mr. Lowton hurried to the door. . . . The object that presented itself to the eyes of the astonished clerk was a boy—a wonderfully fat boy— . . . standing upright on the mat, with his eyes closed as if in sleep. He had never seen such a fat boy, in or out of a traveling caravan; and this, coupled with the utter calmness and repose of his appearance, so very different from what was reasonably to have been expected of the inflicter of such knocks, smote him with wonder.

" 'What's the matter?' inquired the clerk.

"The extraordinary boy replied not a word; but he nodded once, and seemed, to the clerk's imagination, to snore feebly.

" 'Where do you come from?' inquired the clerk.

"The boy made no sign. He breathed heavily, but in all other respects was motionless.

"The clerk repeated the question thrice, and

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receiving no answer, prepared to shut the door, when the boy suddenly opened his eyes, winked several times, sneezed once, and raised his hand as if to repeat the knocking. Finding the door open, he stared about him with astonishment, and at length fixed his eyes on Mr. Lowton's face.



FIG. 1. Thomas Nast's drawing of the fat boy in "The Pickwick Papers."

" 'What the devil do you knock in that way for?' inquired the clerk, angrily.

" 'Which way?' said the boy, in a slow, sleepy voice.

" 'Why, like forty hackney-coachmen,' replied the clerk.

" 'Because master said I wasn't to leave off knocking till they opened the door, for fear I should go to sleep' said the boy."

Figure 1 represents Thomas Nast's drawing of Mr. Wardle's boy, Joe.[3] This masterful description by Charles Dickens of a patient with marked obesity and somnolence is the first complete description of this syndrome that we have been able to find in the literature. For this reason we have called it the Pickwickian syndrome. (Table 1.)

Attention may be drawn to a few recent publications which are also relevant to the particular patient to be presented. In our own laboratories at the Peter Bent Brigham Hospital and at the Boston Lying-In Hospital pertinent observations on pulmonary function in obesity and in pregnancy have been made by Woodbury and by Merriman.[4] Cugell and his colleagues at the Boston City Hospital[5] have made systematic studies of pregnant women and comparable

TABLE 1

CLINICAL FEATURES OF THE PICKWICKIAN SYNDROME

1. Obesity, marked
2. Somnolence
3. Twitching
4. Cyanosis
5. Periodic respiration
6. Polycythemia, secondary
7. Right ventricular hypertrophy
8. Right ventricular failure

studies of patients with ascites have been made by Abelman et al.[6] In general the observations of these workers have indicated that increasing abdominal girth, whether from an enlarging uterus, ascites or obesity, is accompanied by a decreasing expiratory reserve and that when the increase in girth is extreme, it may lead to a state of relative ventilatory insufficiency.

In 1954 Sieker and his colleagues[7] reported on four patients who exhibited extreme obesity and in whom somnolence, periodic respirations, intermittent cyanosis, polycythemia and right axis deviation were also noted. Ventilatory studies showed decreased total lung volume, decreased functional residual capacity and decreased expiratory reserve volume. The study by Sieker et al. is the first modern and scientific description of this syndrome which they named "obesity heart disease." This term appears inaccurate if the heart disease in this group of patients is, as it seems to be in our patient, secondary to pulmonary disease of an unusual variety. This concept will be discussed at greater length. Among the important additions to our knowledge made by these workers was the demonstration that many aspects of this syndrome could be reversed by a sufficient loss of body weight.

A patient similar in many respects to ours was described by Auchincloss et al.[8] This patient was an obese young man who exhibited many of the phenomena presented by our patient. A weight loss of 24 pounds and multiple phlebotomies were followed by a decrease in the dyspnea and edema but not by a disappearance of physiologic abnormalities. Alveolar hypoventilation, arterial hypoxia and hypercapnia were still present.

Weil[9] reported on two patients in whom

obesity and polycythemia were associated and in whom weight reduction was accompanied by a return of the hematocrit to normal. It is probable that most cases in which the association of polycythemia and obesity is present are examples of the Pickwickian syndrome.

CASE REPORT

An example of the syndrome under discussion is presented in the following patient. He was a fifty-one year old business executive who entered the hospital because of obesity, fatigue and somnolence. This patient reported that he had been overweight all his remembered life and for many years had weighed approximately 200 pounds. When this weight was maintained, he was alert, vigorous and able to work long hours. The patient was accustomed to eating well but did not gain weight progressively until about one year before admission. At this time driven, as he said, by anxieties and frustrations he increased his intake of food and began progressively to gain weight. As the patient gained weight his symptoms appeared and became worse. He was unable to give the specific date of the onset of his symptoms but he reported that during the year preceeding admission he had often fallen asleep while carrying on his daily routine; indeed, during the latter part of the year he sometimes found it difficult to distinguish between reality and dreams. He noticed that dyspnea which he had long associated with vigorous exercise was produced by less exertion than formerly and that his breathing was often rapid and shallow even when he was resting. On several occasions he suffered brief episodes of syncope. Persistent edema of the ankles developed. These symptoms which continued in spite of treatment with digitalis, mercurial diuretics and phlebotomy gradually became worse. Finally an experience which indicated the severity of his disability led him to seek hospital care. The patient was accustomed to playing poker once a week and on this crucial occasion he was dealt a hand of three aces and two kings. According to Hoyle[10] this hand is called a "full house." *Because he had dropped off to sleep he failed to take advantage of this opportunity.* A few days later he entered the Peter Bent Brigham Hospital.

Physical examination revealed an extremely obese man, 5 feet 5 inches tall who weighed 263 pounds. He was florid and had cyanosis of the face and nailbeds but no clubbing of the fingers. He was extremely somnolent and several times fell asleep in the middle of a conversation. His eyes would close and he would snore. When roused, however, his mind was clear and his intelligence was obvious. If the patient sat down in a chair, he usually fell asleep promptly and on several occasions fell asleep while standing.

Irregular twitching movements of many muscle groups were observed while the patient was sleeping and during his more active hours. His respirations were variable but generally were shallow and rapid and exhibited a definite tendency to periodicity. This periodic respiration differed from the usual Cheyne-Stokes breathing in that periods of apnea alternated with periods of tachypnea rather than hyperpnea. His general contour was strikingly similar to that of the boy shown in Figure 1.

It was notable that this man in whom cyanosis and abnormal respirations were present had no abnormal physical signs in his lungs. Observation of the patient's chest movements suggested that the extent of these movements was less than normal but the percussion note over the lungs was resonant; the breath sounds although distant were not otherwise abnormal and no rales were heard. The heart was entirely normal on physical examination although the patient's extreme obesity made the examination difficult. The neck veins appeared to be somewhat distended. The liver was demonstrably enlarged, the edge being felt 5 cm. below the right costal margin. The abdomen was extremely obese. Definite edema of the ankles was noted.

A routine neurologic examination revealed no abnormalities of reflexes or of sensation. Electroencephalograms and roentgenograms of the skull were normal. The extreme somnolence was the only abnormal manifestation of the central nervous system. At the time of observation this was so marked that more than once the patient fell asleep in the middle of a sentence.

Laboratory studies were informative. Urine analysis was normal. The hematocrit was 65 per cent. The white cell count, the differential count and the blood smear were normal. Blood chemistry studies indicated no fundamental abnormality of renal or of hepatic function.

The circulation was studied by usual methods. The arterial pressure was 120/90 and the venous pressure was 165 mm. of water. The circulation time (decholin[8]) was 23 seconds. The electrocardiogram at the time of admission showed auricular premature beats, low voltage and an incomplete right bundle branch block.

X-rays of the chest were interesting. Both sides of the diaphragm were elevated; this was especially marked on the right side. The heart was somewhat enlarged in transverse diameter but did not exhibit specific enlargement of any chamber. A curious rounded shadow closely connected with the lower pole of the right hilum was observed. This raised the possibility of a pulmonary arteriovenous fistula but despite laminagrams and angiograms no more accurate definition could be made of this shadow. For approximately six months this shadow has been observed with no evidence of alteration.

Preliminary investigations indicated definite abnormalities of pulmonary function in that this patient had arterial oxygen unsaturation and marked hypercapnia. Therefore further studies were made of pul-

monary function to isolate the physiologic disturbances present and to elucidate their mechanism.

METHODS

Standard methods were used for the determination of lung volumes, functional residual capacity, index of

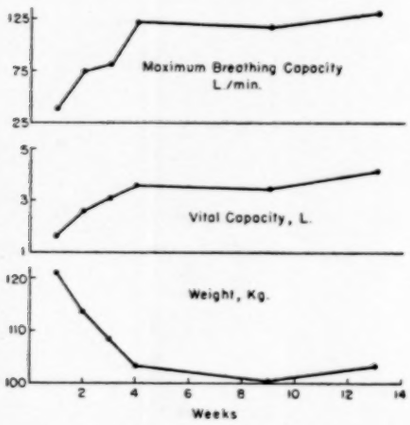


FIG. 2. Changes in pulmonary function with changes in weight.

pulmonary mixing, arterial oxygen saturation and carbon dioxide content, one-second vital capacity and maximum breathing capacity.[11]

The alveolar-arterial oxygen gradient was determined by means of the Riley technic.[12] Pulmonary diffusion was also studied by means of the carbon monoxide single breath method.[13] Physiologic dead space and alveolar ventilation were calculated from the Bohr equation, using arterial PCO_2 as equal to alveolar PCO_2. The sensitivity of the respiratory center to carbon dioxide inhalation was studied by a modification of the technic of West et al.[14] The results of these studies are tabulated in Table II. The various pulmonary functions and related figures are reported: (1) at the patient's original weight, (2) after loss of 17.8 kg. and (3) as values predicted for the patient's height and weight after reduction. The results will be discussed herein. Successive values for some of these measurements during weight reduction are shown in Figures 2 and 3.

Therapy consisted chiefly of enforced weight reduction by means of an 800-calory diet. On this regimen the patient's weight fell from 121.4 to 103.6 kg. in a period of three weeks. As he lost weight his somnolence, twitching, periodic respiration, dyspnea and edema gradually subsided and his physical condition became essentially normal.

INTERPRETATION OF DATA

During weight reduction the total vital capacity increased from 1.6 to 4.2 L. However, the most striking change in lung volumes was in the expiratory reserve volume which increased during weight loss from 0.46 to 1.8 L. It is noteworthy that the residual volume was low (1.66 L.) rather than high and changed insignificantly, rising only to 1.8 L. after weight reduction. This indicated that no significant degree of pulmonary emphysema was present. The functional

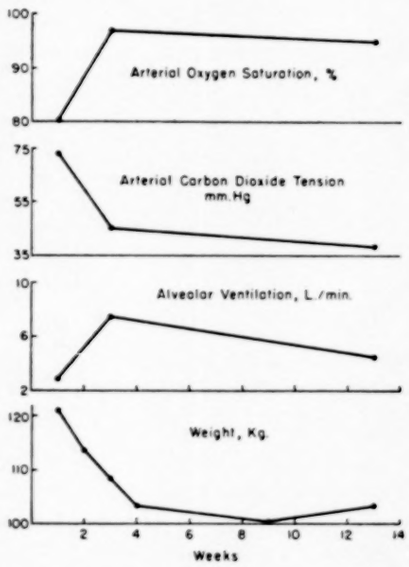


FIG. 3. Changes in arterial blood gas and alveolar ventilation with changes in weight.

residual capacity changed from 2.1 to 3.6 L. and the total lung volume from 3.3 to 6.0 L. The physiologic dead space, which is normally between 150 and 225 ml., was calculated as 372 ml. when the patient entered the hospital and as 147 ml. after weight reduction.

The observations on ventilation are perhaps the most significant. With weight reduction the tidal volume increased from 315 to 365 ml. The total minute volume altered only from 6 L. per minute to 7.3 L. per minute. The significant and perhaps most important finding was an alteration in alveolar ventilation from 2.7 L. per minute to 4.4 L. per minute.

Distribution within the lungs was found to be normal by determination of the index of pulmonary mixing. The diffusion capacity of the lungs by the alveolar–arterial oxygen gradient and by the carbon monoxide single breath method was within normal limits.

The study of arterial blood gases was more revealing. When this patient was first studied, the oxygen saturation of the arterial blood while breathing room air was 80 per cent and after weight reduction was 98 per cent. These studies

were repeated after the inhalation of 100 per cent oxygen for 15 minutes. When the patient was first studied in the obese state, the oxygen saturation rose only from 80 to 97 per cent. It thereby failed to reach the predicted value of 105 per cent; this suggested the possibility of a right-to-left shunt within the heart or lungs.* When this test was repeated after weight reduction, the observed saturation of 106.5 per cent was equal to the predicted value and thus was a strong argument against the presence of a right-to-left shunt.

In view of this observation and the hilar shadow on x-ray it is necessary to consider the possibility that a right-to-left shunt was present before weight reduction and was absent after weight reduction. Considering all the evidence this appears unlikely.

One of the most striking observations concerned the PCO_2 in the arterial blood which was 73 mm. Hg when first observed during the patient's obese state. It fell progressively during weight reduction as shown in Figure 3 and at the end of the period of observation was 37 mm. Hg, a normal figure. While this was taking place the PO_2 in the arterial blood was rising from a low of 52 mm. Hg to a high of 110 mm. Hg, a high normal figure. The pH was slightly below normal when the patient was in the obese state but thoroughly normal after weight reduction.

The changes in the mechanics of breathing were also striking. The spirogram showed no air trapping at any time in either state and the one-second vital capacity was a normal percentage of the total both before and after weight reduction. The maximum breathing capacity, however, showed a striking change. It was 41.5 L. per minute before weight reduction and rose progressively to the essentially normal figure of 133 L. per minute after weight reduction.

The sensitivity of the respiratory center to carbon dioxide stimulation was studied shortly after admission and again after weight reduction. The effects of increased tensions of carbon dioxide on alveolar ventilation are shown in Figure 4. It is clear that at the time of admission when the patient had a high arterial PCO_2 the sensitivity of the respiratory center was far below the normal level. However, after weight reduction this patient responded in an essentially normal manner.

These observations are of importance for three

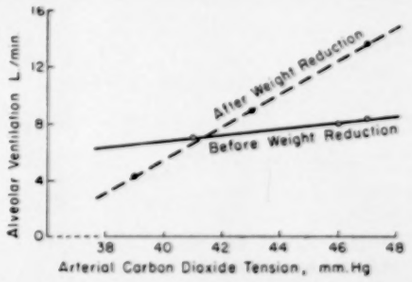


FIG. 4. Respiratory center "sensitivity" to carbon dioxide before and after treatment. Each point represents the alveolar ventilation at an observed arterial carbon dioxide tension.

reasons: (1) They rule out a central lesion involving the respiratory center as the cause of this patient's hypoxia and hypercapnia. (2) They demonstrate the fact that prolonged exposure to high levels of carbon dioxide produces adaptation so that an increase in arterial PCO_2 no longer produces a normal augmentation of ventilation. This response to increased arterial PCO_2 has been categorized as a "diminished respiratory center sensitivity." (3) They illustrate that this diminished respiratory center sensitivity can be reversed by decreasing arterial PCO_2 to a normal level.[16]

These studies enable us to rule out for all practical purposes such chronic pulmonary diseases as fibrosis, emphysema or chronic bronchial disorder. Against the presence of any one of these we cite the following points: (1) the absence of cough, sputum and wheezing, (2) the normality of the lungs on physical examination, (3) the absence of signs associated with emphysema on the x-ray film, (4) the fact that the lung volumes and the pattern of ventilation do not fit the diagnosis of emphysema or pulmonary fibrosis, (5) the normal level of pulmonary diffusion when studied by the carbon monoxide single breath method and by the alveolar–arterial gradient and (6) the normal level of the index of pulmonary mixing.

These findings enable us also to rule out a pulmonary arteriovenous shunt as a major factor in the situation, since the alveolar ventilation is low rather than high and the arterial carbon dioxide tension is high rather than low.

* The failure to achieve full saturation on the inhalation of 100 per cent oxygen for 15 minutes has been reported as indicating the presence of an anatomic right-to-left shunt.[15] This is usually the case but it has been our experience that patients with severe pulmonary disease may also exhibit undersaturation on 100 per cent O_2 inhalation for 15 minutes. With improvement in the pulmonary status full saturation may then be attained. Our patient is an example of this phenomenon.

TABLE II
PULMONARY FUNCTION STUDIES

	Before Weight Reduction	After Weight Reduction	Predicted After Reduction
Weight (kg.)	121.4	103.6	.....
Lung Volumes (BTPS)			
Inspiratory capacity L.	1.20	2.40	3.60
Expiratory reserve volume, L.	0.46	1.80	1.20
Vital capacity, L.	1.64	4.20	3.80
Residual volume, L.	1.66	1.83	1.80
Functional residual capacity, L.	2.12	3.63	2.40
Total lung volume, L.	3.32	6.03	6.00
Dead space, physiologic, ml.	372	147	150–225
Ventilation (BTPS)			
Tidal volume, ml./breath	315	365	.....
Frequency, breaths/min.	19	20	.....
Minute volume, L./min.	6.0	7.3	.....
Alveolar ventilation, L./min.	2.7	4.4	4.5
Oxygen consumption, resting, ml./min. STPD	405	242	.....
Distribution			
Pulmonary mixing index, % nitrogen in expired gas	1.49	0.37	<1.5
Diffusion			
Alveolar-arterial oxygen gradient, mm. Hg	0	.....	0–15
Carbon monoxide, single breath, ml. CO/min./mm. Hg	23	.....	15–40
Arterial Blood			
Oxygen saturation, %, air	80	98	>95
Oxygen saturation, %, 100% oxygen	97	106.5	105
Carbon dioxide tension, mm. Hg	73	37	35–40
Oxygen tension, mm. Hg	52	110	100
pH	7.31	7.41	7.35–7.45
Mechanics of Breathing			
Maximum breathing capacity, L./min.	41.5	133.0	122.0
Air trapping	None	None	None
Vital capacity, one sec., % of total	81	83	>75
Respiratory Center Sensitivity			
Increase in alveolar ventilation per unit increase in arterial carbon dioxide tension L./min./mm. Hg	0.065	1.32	1.30

We can conclude at this point that the major physiologic abnormality demonstrated was an inadequate alveolar ventilation.

PHYSIOLOGIC MECHANISMS

A low alveolar ventilation leads to a low alveolar oxygen and a high alveolar carbon dioxide and therefore explains the arterial blood gas tensions in this patient. It seems reasonable to conclude that inadequate alveolar ventilation caused this patient's chronic hypoxia and chronic hypercapnia. These in turn could produce cyanosis and the resultant polycythemia, somnolence, periodic breathing, and the other symptoms and signs present in this patient.

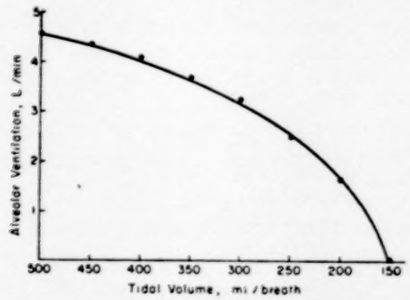


FIG. 5. The effect of decreasing tidal volume on alveolar ventilation, assuming a constant minute volume and a constant dead space.

If, as appeared possible, the hypoventilation of the alveoli was due to the increase in weight, then the final test would be the effect of weight reduction on the pulmonary functions and the general status of the patient. It does appear from a study of Table II and Figures 2, 3 and 4 that weight-reduction was followed by an improvement in the level of alveolar ventilation and by a restoration of the various values relating to pulmonary function to essentially normal levels.

It is now necessary to consider whether or not there is any reason to believe that extreme and progressive obesity can lead to subnormal alveolar ventilation and so set in motion the complicated course of events and the results observed in this patient. It is known that obesity leads to a low expiratory reserve volume and to a diminished functional residual capacity. These changes have certain practical disadvantages in that they deprive the patient of certain buffer mechanisms normally available and permit unusual fluctuations in the blood gases. It has been observed[4] that, by some mechanism, in patients with a high degree of obesity there is a tendency to shallow respiration. The precise mechanism by which obesity leads to shallow respiration is not known. Butler and Arnott[18] have shown that below the usual level of respiration, that is, as the lung approaches the expiratory position, the work of breathing increases. Therefore the obese man with a diminished expiratory reserve volume will do more work than is normally required to maintain his alveolar ventilation. Such an increase in work may conceivably lead to a change in the type of breathing. If this work demand or some other change associated with obesity can lead to shallow respiration, then the rest of the sequence leading to alveolar hypoventilation is not difficult to explain.

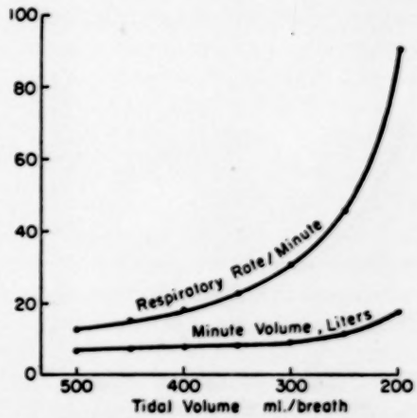


FIG. 6. Calculated respiratory rate and minute volume necessary to maintain a constant alveolar ventilation as tidal volume decreases.

Shallow breathing leads to alveolar hypoventilation because ventilation of the anatomic dead space must occur before alveolar ventilation can take place. By the Bohr equation: alveolar ventilation per breath = tidal volume − dead space ventilation per breath. Therefore at a constant minute volume any reduction of tidal volume will mean an automatic reduction of alveolar ventilation. This is shown graphically in Figure 5. An anatomic dead space of 150 ml. and a constant minute volume of 6.5 L. are assumed. Despite the maintenance of a constant minute volume by an increased respiratory rate, alveolar ventilation falls as tidal volume falls that is, as breathing becomes more shallow.

When the reduction of tidal volume reaches a critical point, the maintenance of alveolar ventilation by means of increased respiratory rate becomes impossible. (Fig. 6.) In this figure the

respiratory rate and minute volume necessary to maintain normal alveolar ventilation have been calculated on the assumptions that anatomic dead space is 150 ml. and that alveolar ventilation is 4.55 L. per minute. As tidal volume becomes less than 250 ml. respiratory rates greater than 40 per minute become necessary. Although it has been shown that even at tidal volumes which are smaller than dead space volume some alveolar ventilation takes place,*[18] it can be seen that continued shallow respiration means eventual alveolar hypoventilation. For example, it is generally accepted that when patients in tank respirators are forced to rapid and shallow breathing alveolar hypoventilation develops resulting in high levels of carbon dioxide and low levels of oxygen.

It is suggested that periods of shallow breathing may develop under the mechanical conditions existing in obese patients, and that such periods of shallow breathing may in some patients set off a progressive and vicious cycle which in extreme cases may lead to the pitiable state in which this patient presented himself. At any rate, there is accumulating evidence that in some individuals there is a critical degree of obesity at which ventilatory insufficiency appears.

The heart disease manifested by this patient was clearly related to his underlying pulmonary disease. The peripheral edema, venous hypertension, hepatomegaly and even the incomplete right bundle branch block disappeared as the patient lost weight and his pulmonary status improved. Thus this form of heart disease is properly classified as a form of cor pulmonale. The return to normal of this patient's pulmonary and cardiac status makes this syndrome an example of curable heart and lung disease.

SUMMARY

The association of alveolar hypoventilation with obesity is described. The literature relating to the clinical manifestations of this association is reviewed.

A patient is presented in whom these phenomena are illustrated. The physiologic defects present were isolated by means of pulmonary function tests. Reversal of these defects was achieved by means of weight reduction.

* Maintenance of alveolar ventilation when tidal volume is less than dead space volume is accomplished by two mechanisms: (1) centrally placed alveoli with a dead space less than 150 ml., (2) inspired air travelling as a cone front rather than as a square front.

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A Peculiar Type of Cardiopulmonary Failure Associated with Obesity*

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THERE have been several recent reports of patients with extreme obesity associated with cyanosis, polycythemia, hypercapnia and right-sided heart failure without recognizable heart or lung disease.[1-3] This is an account of two similar patients, one of whom was examined postmortem.

CASE REPORTS

CASE 1. J. E. (Johns Hopkins Hosp. Hist. No. 161770), a white man who was forty-eight years old when he died, was admitted to the hospital four times between 1942 and 1954, complaining of dyspnea and severe swelling of the ankles. Except for intermittent bursitis of the left subacromial joint, the patient's difficulty had been associated with obesity and heart failure.

He was of German stock. His mother weighed 250 pounds and his father 270 pounds. The patient ate large amounts of pork chops, potatoes and bread. At the age of five, he was known as "Fatty." At the age of fifteen, he weighed 150 pounds; at thirty, 296; at thirty-two, 367 and at thirty-five, 420 pounds. In 1939, when he weighed 371 pounds, his blood pressure was 140/100 mm. Hg (small blood pressure cuff). Examination was not remarkable except for obesity. The urine showed a trace of albumin, the phenolsulfonphthalein excretion was 62 per cent in two hours. The hematocrit was 49. The patient was thoroughly studied at this time but no cause other than overeating could be found for the obesity. He remained well until March, 1941, when he began to have exertional dyspnea. This was followed by rather sudden edema of the ankles and increase in weight. He was treated with ammonium chloride alone with moderate success. In January, 1942, however, the dyspnea became worse and he gained thirty pounds in the next month. Because of lack of response to diuretics, he was admitted to the hospital.

On the first admission (February 9 to April 4, 1942) the patient was extremely obese. The blood pressure was 130/80 mm. Hg (large blood pressure cuff) and was never elevated on subsequent determinations. There was marked brawny edema of the legs. Slight cyanosis was noted. The heart was enlarged, the sounds were distant, the rhythm was regular and no murmurs were heard. There were expiratory high pitched dry rales but no moist rales were heard. The physical examination and laboratory data were otherwise normal except for an erythrocyte count of 6.4 million per cu. mm., hemoglobin 16 gm. % and hematocrit 56%. X-rays revealed a grossly enlarged heart. The venous serum carbon dioxide content was 30.4 mEq./L. The urine was normal and the phenolsulfonphthalein excretion was 90 per cent in two hours. The electrocardiogram was normal except for a PR interval of 0.22 seconds.

Digitalis was administered to the patient, he was placed on a low salt diet and given mercupurin. On this regimen the venous pressure fell from 235 mm. of saline on admission to 90 mm. during the second week. The weight fell from 420 to 365 pounds in the first week and at the time of discharge the patient weighed 335 pounds.

During the next four years the patient felt well on a regimen of digitalis and intermittent ammonium chloride and was able to work as a machinist. He was readmitted in 1948 because of increasing dyspnea and edema of the ankles which did not respond to weekly injections of mercupurin and 0.4 gm. digitalis daily.

At the time of the second admission (May 30 to June 28, 1948) the patient weighed 355 pounds. Marked purplish cyanosis was now noted. Moderate orthopnea was observed. The lungs were clear. The heart rhythm was irregular, the heart was enlarged but no murmurs were present. Liver dullness was percussed 8 cm. below the right costal margin. Marked pitting edema was present. Clubbing of the fingers was noted for the first time. The erythrocyte count was 8.3 million, the hemoglobin 23.5 gm. and the hematocrit 70. On admission the venous serum carbon dioxide content was 35 mEq./L. The electrocardiogram showed auricular fibrillation with right axis deviation.

The treatment and response were similar to those on the previous admission except for the development of jaundice. The bilirubin rose to 5.9 mg. per cent on the seventh hospital day and subsequently declined to 1.8 mg. per cent at the time the patient was discharged. The thymol turbidity was 7.7 units and the

* From the Johns Hopkins Medical Service, Baltimore City Hospitals, Baltimore, Maryland.

TABLE I
STUDIES ON CASE I

	Vital Capacity (L.)	Maximum Breathing Capacity (L./min.)	Arterial Oxyhemoglobin Saturation (%)	Hematocrit (%.)	Weight (lb.)	Electrocardiogram
Predicted Values	3.860	112	96+	42 ± 5	...	.....
Date:						
1939	.....	...	.....	49	371	.....
1942	.....	...	.....	56	420	Normal
1948	1.3	...	63	70	355	Auricular fibrillation, right axis deviation
1952	1.4	33	86	.....	...	.....
1953	.....	...	.....	39	328	.....
1954	.....	...	.....	49	287	Auricular fibrillation, right ventricular hypertrophy

cephalin flocculation test 3 plus. The bromsulphalein® retention was 55 per cent in thirty minutes. All these values had returned to normal by the time the patient was discharged. Studies of the arterial blood on the second hospital day showed that the whole blood carbon dioxide content was 23.3 mEq./L. and the oxyhemoglobin saturation was 63 per cent. The vital capacity was 34 per cent of the predicted value. (Table I.)

Attempts to revert the auricular fibrillation to sinus rhythm with quinidine were unsuccessful. A total of 6,500 cc. of blood was withdrawn and at the time the patient was discharged the hematocrit was 50. When discharged from the hospital, he weighed 289 pounds. The patient was then followed continuously in the cardiac clinic. He required digitalis, constant efforts to maintain a low salt and low caloric diet and frequent mercurial diuretics and phlebotomies.

Repeated studies were made in an attempt to diagnose the patient's heart disease. Early in 1952 a pneumotachogram showed abnormally slow velocity of air flow during inspiration and expiration. No abnormality of bronchial resistance could be demonstrated by determining alveolar pressures.[4] At this time the arterial blood oxyhemoglobin saturation was 86 per cent on room air and 94 per cent on 100 per cent oxygen. The vital capacity was 37 per cent and the maximal breathing capacity 29 per cent of predicted values. The total lung capacity was 65 per cent of the predicted value and the residual volume was 47 per cent of the total capacity.[5] (Table II.)

Despite continuous treatment in the outpatient department, edema began to recur and the patient was readmitted to the hospital.

On the third admission (March 23 to April 4, 1953) the results of the examination did not differ greatly from those on previous occasions except for more intense cyanosis and plethora, more edema with ascites and scrotal swelling. A few coarse expiratory wheezes were present and auricular fibrillation persisted. He weighed 328 pounds on admission and 251 pounds when discharged. The venous serum carbon dioxide content was again elevated at admission (32.2 mEq./L.) and fell during the first week (28.4 mEq./L.). Following discharge the patient felt well for approximately one year but again dependent edema began to develop and he was readmitted to the hospital.

On the fourth admission (April 15 to June 4, 1954) no essential change had occurred since the previous admission. The blood pressure was 92/70 mm. Hg. Cyanosis was marked, and clubbing was more prominent. A moderate number of medium moist rales were heard over the lower portion of the chest. The heart was enlarged both to the right and left. The rhythm was completely irregular with a pulse deficit of 10 beats. The second pulmonic sound was accentuated. A grade 2 systolic murmur was heard at the apex. Peripheral edema was extreme. The patient was treated with the usual measures and with diamox.® The electrocardiogram showed more marked right axis deviation, auricular fibrillation, right ventricular hypertrophy and low voltage. With treatment the weight dropped from 287 to 213 pounds.

During this admission there was persistent 2 plus albuminuria. The phenolsulfonphthalein test showed 55 per cent excretion in two hours. White and red blood cells were found on repeated urine examinations. A left renal calculus was demonstrated on the flat plate of the abdomen.

The patient returned to the outpatient department and seemed to be doing well on large doses of mercurials, digitalis, low salt diet and diamox. When last seen on February 17, 1955, he appeared well. On March 7, 1955, he suddenly became sick, was taken to the accident room of another hospital and was dead on arrival.

At autopsy the body weighed 246 pounds. There was moderate peripheral pitting edema of the legs. The abdominal cavity contained 300 cc. of pale yellow fluid, and the thoracic cavities contained 200 cc. of fluid on both sides. There were a few fibrous adhesions at the apexes and no excessive pericardial fluid.

The heart weighed 700 gm. There was marked dilatation and hypertrophy of the right atrium and right ventricle. The average thickness of the left ventricular wall was 17 mm. and of the right ventricular wall 8 mm. The valves were normal in appearance with normal circumferences. There was no excessive fat around the heart. The foramen ovale was closed. The coronary arteries were widely patent and no myocardial lesions were seen. The lungs together weighed 1,900 gm. The blood vessels were normal. Scattered areas of consolidation were present throughout both lungs. The liver weighed 1,900 gm. and on section was nutmeg in appearance. The spleen measured 19 cm. by 5 cm. and weighed 720 gm. The capsule was taut, the pulp was red and the architecture obscure. The kidneys were grossly normal but there were small black friable stones in the calyces of both kidneys. No infection or dilatation of the pelvis of the kidney was observed.

Microscopic examination of the organs revealed no abnormalities except for diffuse bronchopneumonia and an acute splenic tumor. In particular there were no abnormalities of the myocardium or the vessels of the lungs. No evidence of emphysema was observed.

Death was believed to have been caused by diffuse bronchopneumonia and heart failure although the right ventricular hypertrophy was unexplained.

Both parents of this forty-eight year old patient were extremely obese. The patient was a heavy eater and had been obese all his life. At the age of thirty-five he began to have exertional dyspnea and right-sided heart failure. At this time cyanosis and polycythemia were noted. The cardiac failure responded well to digitalis, diuretics and a low salt diet but over the next thirteen years the cyanosis and polycythemia increased. The heart enlarged and auricular fibrillation became established. Finally, right axis deviation appeared on the electrocardiogram although it had been normal previously with the same degree of obesity. Clubbing of the fingers appeared. Following the patient's discharge in 1948 the hematocrit was maintained near normal with repeated phlebotomies. Carbon dioxide retention occurred. Death was apparently caused by bronchopneumonia and heart failure.

CASE II. V. I. (Baltimore City Hospitals Hist. No. 197362), a fifty-four year old ice salesman who had been incapacitated by obesity for the past fifteen years, entered the hospital on May 10, 1955, because of progressive edema of the ankles and exertional dyspnea of seven months' duration. No one in the patient's immediate family was obese. A twin brother had a normal body build. The patient weighed 130 pounds at seventeen years of age and 140 pounds at thirty. After this he began to gain weight rapidly and at the age of thirty-eight weighed 225 pounds. He had a tremendous appetite which he satisfied with large meals. He was wont to supplement his diet with six to eight ice cream cones daily.

TABLE II
LUNG VOLUME MEASUREMENTS OF CASE I, MAY 21, 1952

	Observed Values	Predicted Values
Vital capacity (L., BTPS)	1.440	3.860
Expiratory reserve volume (L., BTPS)	0.302	.....
Residual volume (L., BTPS)	1.530	1.510
Total lung capacity (L., BTPS)	3.270	5.040
Residual volume (% of total capacity)	47	30
Maximum breathing capacity (L./min., BTPS)	38	112

Note: The ratio of high residual volume to total capacity is not caused by a high residual volume but by a low total lung capacity. BTPS = Body temperature, ambient barometric pressure, saturated at body temperature.

Except for obesity the patient had been well until seven months before admission. At that time he began to gain weight rather rapidly and at the same time noted exertional dyspnea and swelling of the ankles. There was moderate orthopnea for four months but no paroxysmal nocturnal dyspnea.

The vital signs were normal except for a respiratory rate of 32. The blood pressure was 140/75 mm. Hg in both arms (small blood pressure cuff). On admission he weighed 395 pounds and was 66 inches in height. The patient was so obese he was unable to sit up in bed or turn over. He was plethoric and cyanotic. Examination of the lungs showed that inspiration was prolonged with some wheezing and rales. The heart was believed normal in size, the rhythm was regular and no murmurs were heard. The abdominal wall was edematous and ascites was present. The skin of both legs was thick and dark red with pitting edema up to the sacrum. At the time of admission the urine and blood examinations were not remarkable except for a hematocrit which ranged around 57 and a venous serum carbon dioxide content of 34.2 mEq./L.; subsequently these values returned to normal. The electrocardiogram showed right axis deviation with low T waves. The X-ray of the chest initially showed an enlarged heart with pulmonary congestion.

The patient was treated with bed rest, a low salt, low caloric diet, digitalis and occasional mercurial diuretics. There was no somnolence or Cheyne-Stokes

TABLE III
STUDIES ON CASE II

	Date						Predicted Values	Normal Values for Arterial Blood
	5/13/55	5/19/55	5/26/55	6/3/55	6/7/55	6/27/55		
Weight	376	342	333	321	320	305		
I. Spirometry:								
Vital capacity (Liters, BTPS)	1.09	1.88	2.55	2.57	2.81	2.88	3.59	
Maximum breathing capacity (Liters per minute, BTPS)	36	79	89	98	101	103	95	
II. Arterial blood gases:								
pO_2	33	51	52		71	70		90 mm. Hg
pCO_2	58	53	46		44	44		40 ± 3 mm. Hg
CO_2 content, blood	22.96	24.91	22.97		21.71	22.82		22 ± 2 mEq./L.
Hematocrit	55	57	57		52	53		42 ± 5 mm.
pH	7.29	7.37	7.39		7.39	7.43		7.40 ± .04
Buffer base	57	50	51		50	52		50 ± 4 mEq./L.
III. Pulmonary distribution studies:								
O_2 Intake	147		153	147	143	142		129 L./min./M_2
Ventilation	4.31	3.44	3.48	3.32	3.62	3.66		3.2 L./min./M_2
$\frac{\text{Dead space ventilation}}{\text{Total ventilation}}$					37%	38%		30%
$\frac{\text{Venous admixture}}{\text{Total blood flow}} \times 100$					5–11%*	6–13%*		6%

Note the rise in vital capacity, maximal-breathing capacity, arterial blood oxygen tension and fall in carbon dioxide tension with fall in weight.

* Since A-V difference was unknown, values were determined at assumed A-V differences of 30 and 70 per cent saturation.[15]

breathing. There was a rapid initial diuresis with disappearance of the peripheral edema. He was discharged on June 29, 1955, after a total weight loss of 95 pounds in forty-nine days.

This fifty-four year old man was not excessively obese as a child and had no excessively obese relations. He had had a tremendous appetite for at least thirty years. Heart failure developed at the age of fifty-four. The heart failure was unusual in that it was predominantly right-sided, was associated with cyanosis, polycythemia, right axis deviation in the electrocardiogram and carbon dioxide retention.

Physiologic studies (Table III) initially showed respiratory acidosis caused by alveolar hypoventilation. Severe arterial blood oxyhemoglobin unsaturation was observed. The dead space on later examinations was found to be increased. Venous admixture[6] was also increased. Studies of bronchial resistance with esophageal pressures and air flow studies[7] demonstrated no evidence of abnormal lung elasticity or obstructed air flow. The vital capacity and maximal breathing capacities, which were decreased on the initial study, returned to normal, although it is possible that the vital capacity remained slightly depressed.

COMMENTS

Newman, Feltman and Devlin[1] described five patients with polycythemia who had arterial blood oxyhemoglobin unsaturation and hypercapnia. Two of these patients (Cases 4 and 5) were obese and were so similar to the patients described in this article that one wonders whether they were actual cases of polycythemia vera. Newman suggested that the reduction in lung volumes was secondary to changes in lung elasticity and viscous resistance caused by polycythemia.

Sieker, Estes, Kelser and McIntosh[2] reported

on four patients quite similar to the ones we have described. They explained the development of the syndrome on the basis of low functional residual capacity and reduced sensitivity of the respiratory center. Auchincloss, Cook and Renzetti[3] believed that increased work of breathing or reflex reduction in tidal volume might be the initiating factor which all other findings might follow.

The clinical and physiologic observations on our two patients were quite similar. Both had been obese for several years before heart failure developed. None of the common causes of heart failure could be demonstrated in either patient. Reduction in vital capacity occurred without any suggestion of emphysema. Anoxemia and hypercapnia were severe during heart failure but tended to improve with cardiac compensation. Right axis deviation was present in one patient when first seen and developed in the other under observation. Clubbing of the fingers was prominent in the first patient. Autopsy of the first patient failed to reveal any of the usual causes of heart failure, cyanosis or hypercapnia.

No obvious explanation for the heart failure in these patients can be drawn from the clinical or autopsy findings. It is possible, however, to postulate certain physiologic abnormalities secondary to obesity which may have led to the clinical picture. Both patients had chest walls which scarcely moved with deep respiration. This lack of motion may have been caused by the heavy fat pads which immobilized the rib cage like a binder. The long fixation of the chest wall in one position may have been conducive to fixation of the ribs at their cartilagenous junctions, thus further limiting motion.

It was repeatedly noted that the patients had predominant abdominal breathing. Although the second patient on fluoroscopy had normal diaphragmatic motion and normal maximal breathing capacity when completely compensated, this motion was brought out only by intensive urging over short periods of time. Since large amounts of abdominal fat had to be moved with the diaphragm, it may be postulated that breathing in these patients required a greater expenditure of energy than under normal circumstances.

That the breathing was also inefficient in aerating the lungs can be adduced from the tendency toward hypercapnia. Since the level of carbon dioxide pressure in the arterial blood is closely related to alveolar ventilation, it can be concluded that alveolar hypoventilation was present.[8] This observation was most marked in the second patient in whom improvement was demonstrated serially as cardiac compensation occurred. With severe alveolar hypoventilation a lowering of the alveolar oxygen tension and a fall in the arterial blood oxyhemoglobin saturation occur.[9] A rise in the pulmonary artery pressure may also be associated with a low alveolar oxygen tension.[10]

In addition to the generalized alveolar hypoventilation poor distribution of the inspired air was indicated by the presence of a physiologic shunt in both patients.[11] This physiologic shunt was demonstrated in the first patient by measuring arterial blood oxygen tension while he was breathing pure oxygen. In the second patient such a shunt was demonstrated at the time of optimal cardiac compensation when hypercapnia was no longer present. These observations suggest that in addition to generalized alveolar hypoventilation there was inhomogeneity of distribution of inspired air.[11]

Both of these factors probably contributed to the arterial blood oxyhemoglobin unsaturation. This abnormality in turn brought about polycythemia[12] and an increased blood volume. It may be assumed that coronary artery blood oxyhemoglobin unsaturation was present. The heart therefore was called upon to pump more blood, against an increased pulmonary artery pressure with a less efficient oxygen supply. Under these circumstances right ventricular hypertrophy might be expected to occur, with the development of electrocardiographic changes and finally right-sided heart failure.

This train of events is an adequate explanation of the condition found if we are able to explain how the hypercapnia was allowed to develop in the presence of a mechanical system, which was able to produce enough alveolar ventilation to return the carbon dioxide tension to normal. A rise in carbon dioxide tension is the normal stimulus to breathing. It has been stated that in the second patient the diaphragms were seen to move normally and with compensation; the maximal breathing capacity was normal. When the maximal breathing capacity is normal, the subject generally is able to produce enough alveolar ventilation to bring the carbon dioxide tension to normal during rest. How then did hypercapnia develop when an adequate mechanism was present to prevent it? The explanation here is the same as that used to

explain the hypercapnia of obstructive emphysema[13] or respiratory poliomyelitis with inadequate chest muscles[9]—the amount of work necessary to keep the carbon dioxide pressure at a normal level continually is so great that the body compromises and allows the carbon dioxide to rise rather than put out the continuous excess effort necessary to keep the carbon dioxide at a normal level. We have seen this situation in a patient with bilateral fibrous pleurisy and without emphysema. Hypercapnia has also been described in patients with kyphoscoliosis without emphysema.[14]

SUMMARY

Two patients are reported on who were extremely obese, had fixed chest walls, abdominal breathing, low vital capacities, hypercapnia, hypoxia, polycythemia, right axis deviation and right-sided heart failure. On postmortem examination one patient was found to have died of bronchopneumonia but to have no cardiac abnormality except dilatation and hypertrophy of the right auricle and ventricle.

The etiology of this cardiopulmonary syndrome in extremely obese persons is discussed.

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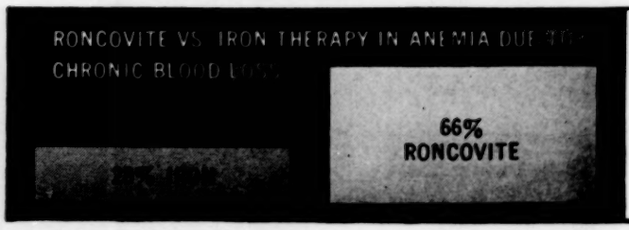
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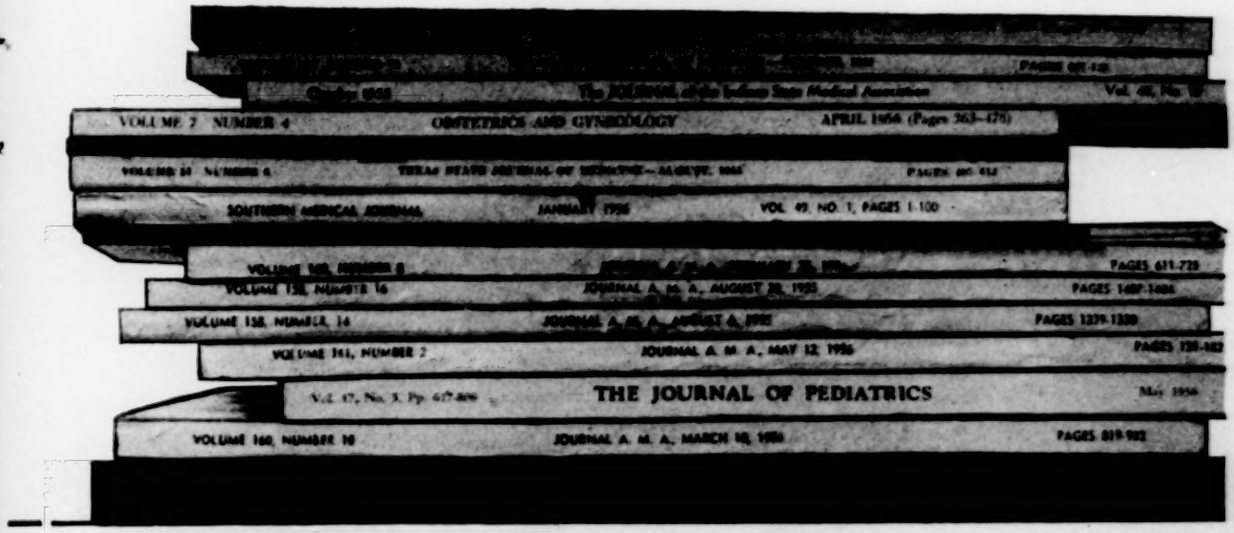
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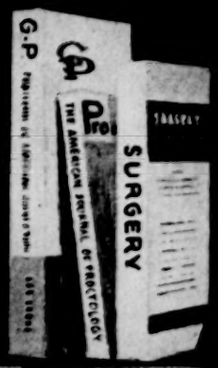
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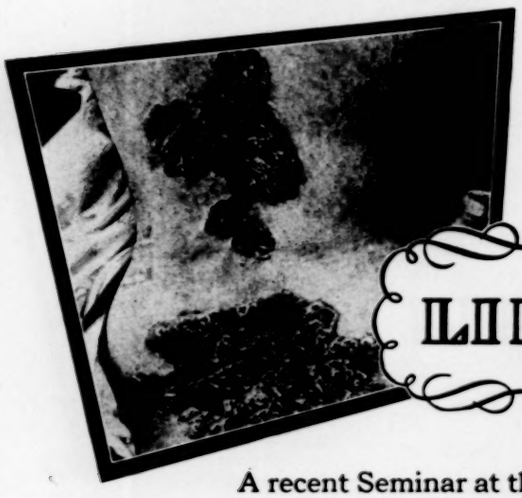


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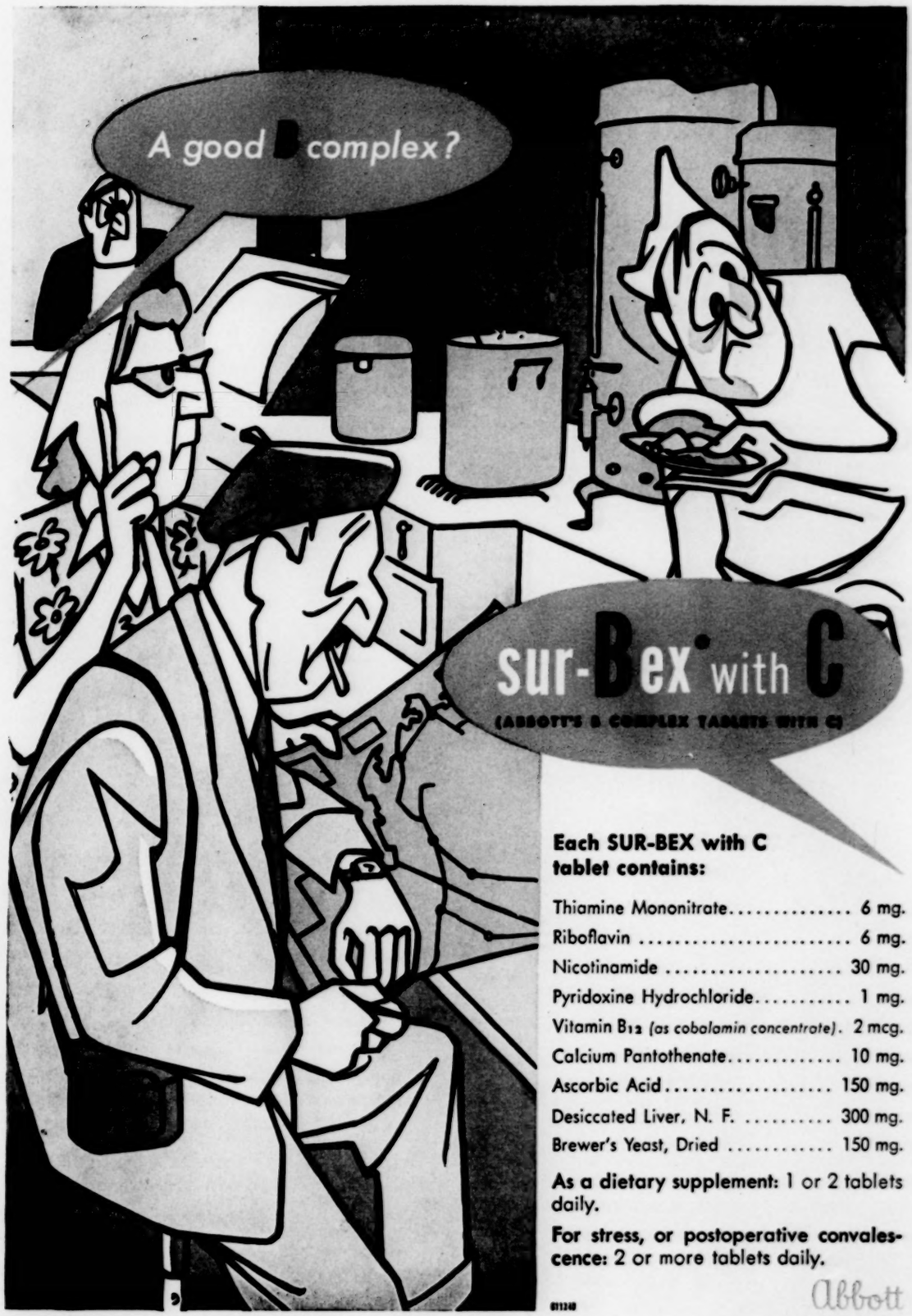
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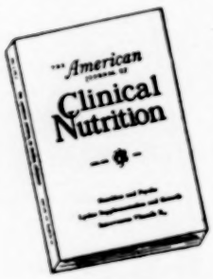
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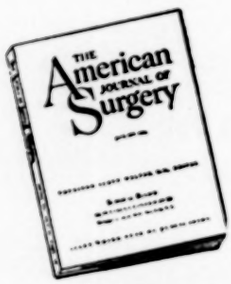
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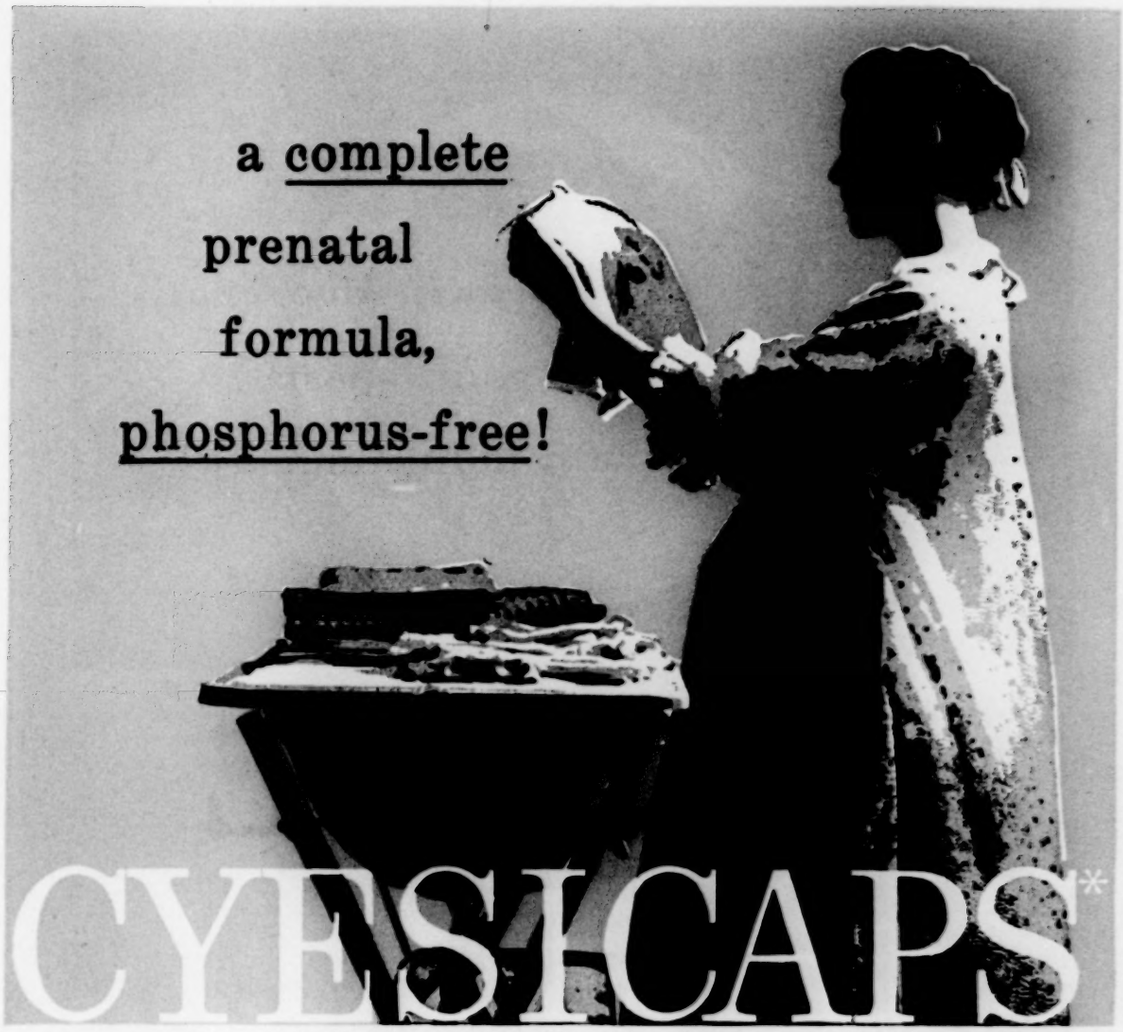
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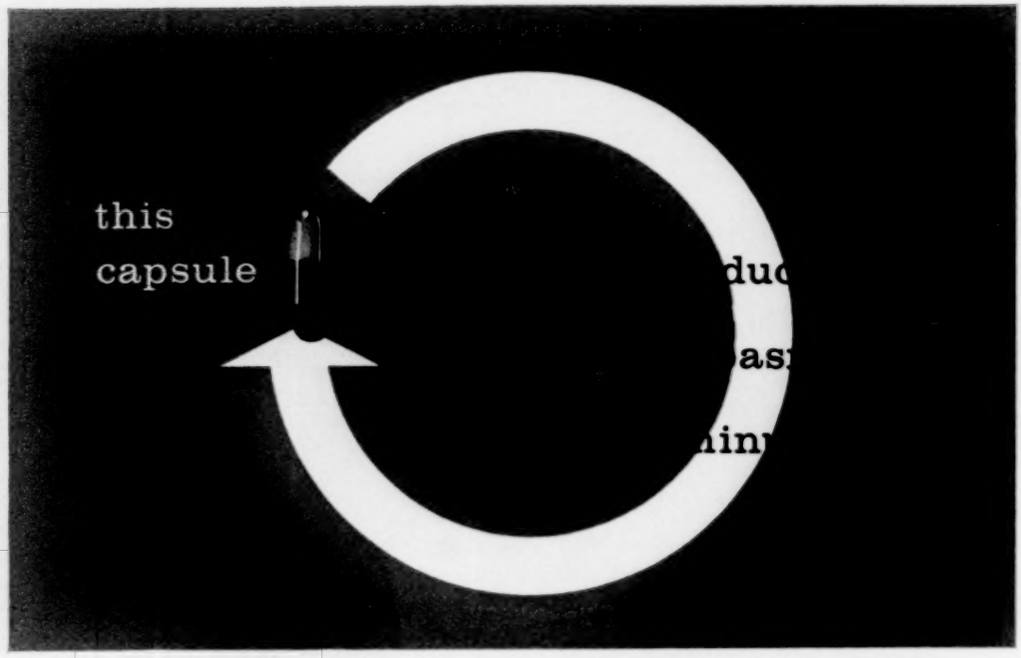
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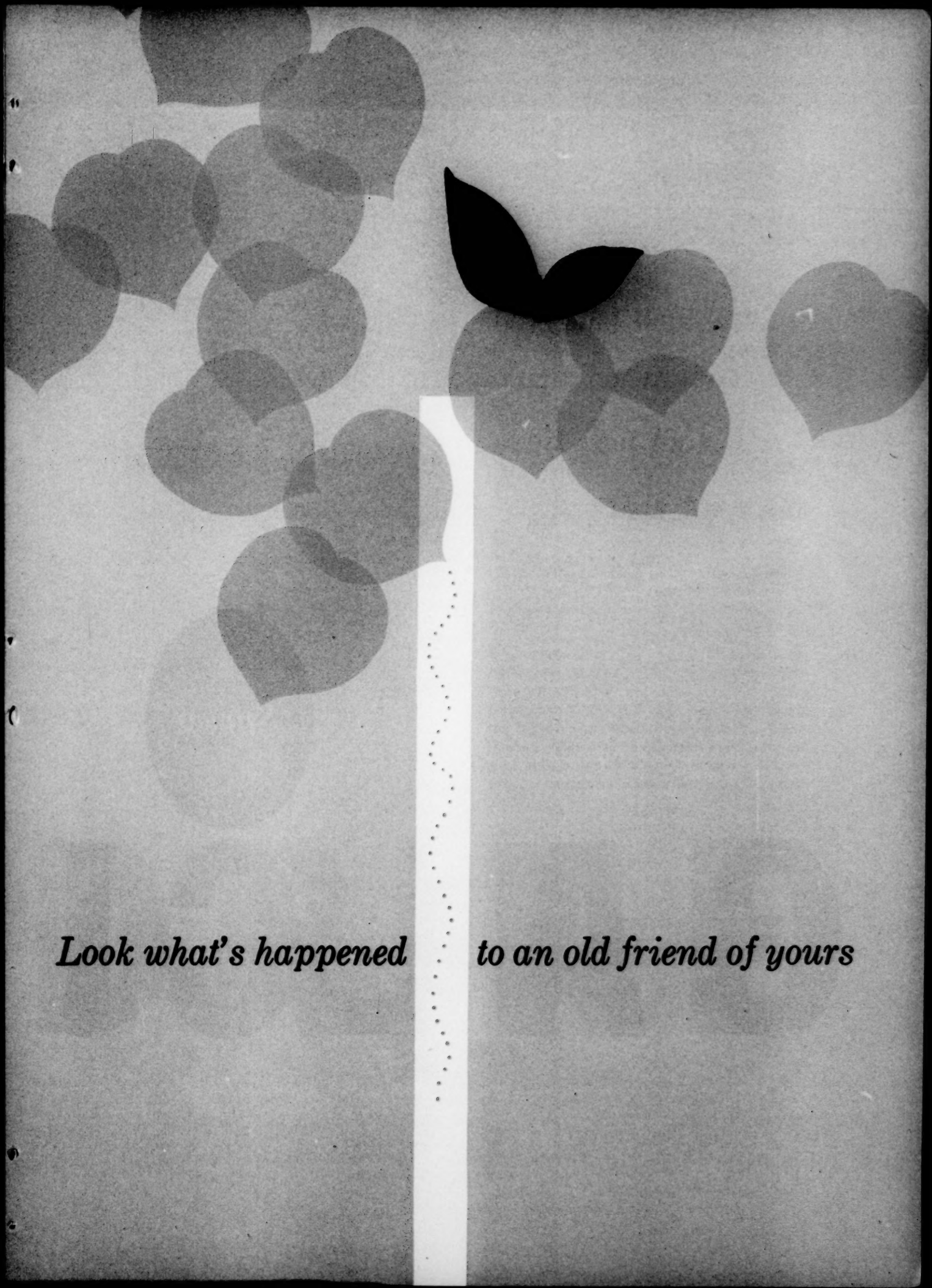


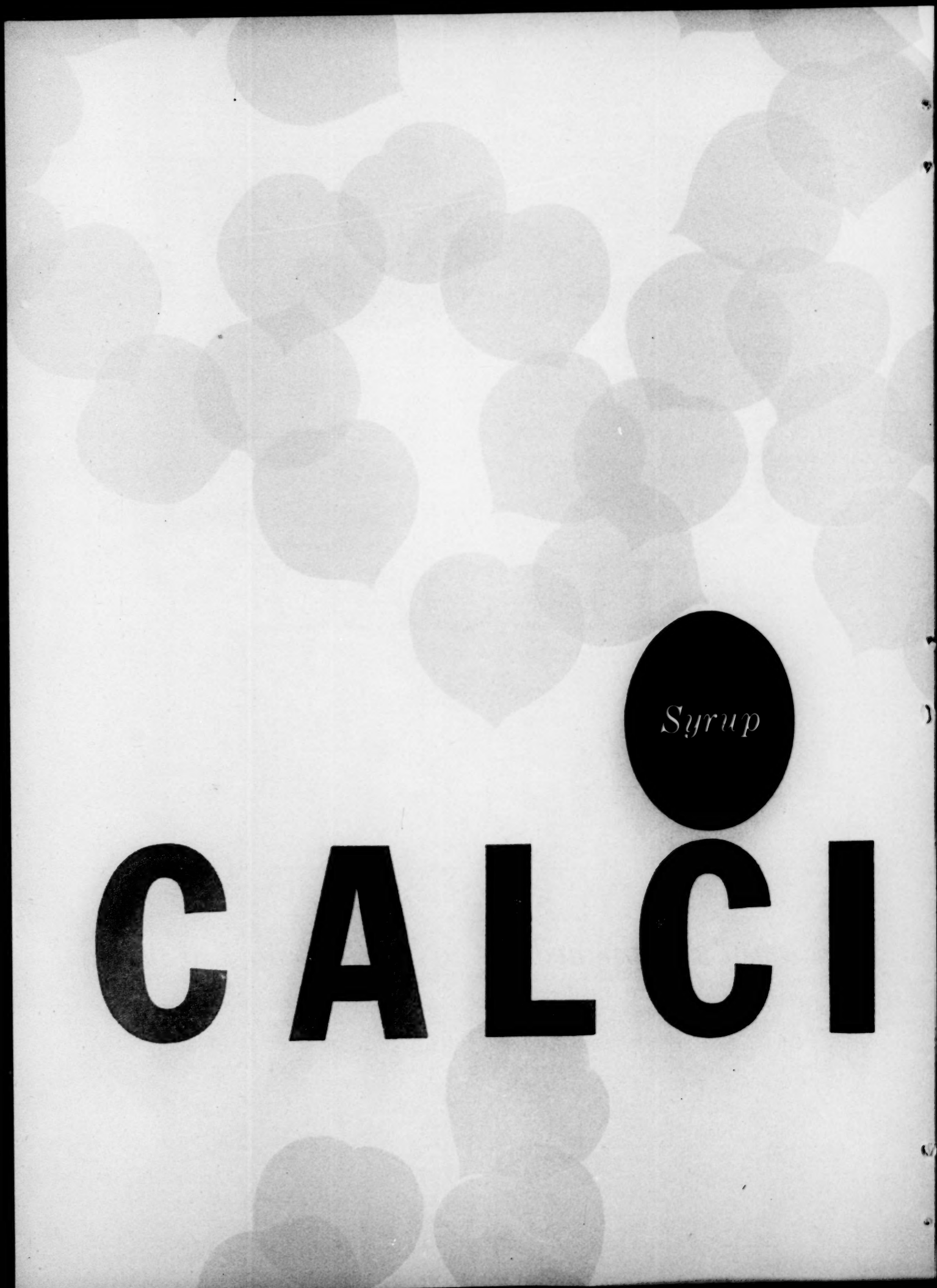
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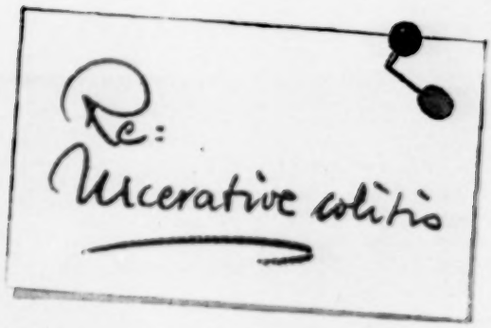
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1. BARGEN, J. A.: "Present Status of Hormonal and Drug Therapy of Ulcerative Colitis", South. M. J. *48*: 192 (Feb.) 1955.
2. BARGEN, J. A. and KENNEDY, R. L. J.: "Chronic Ulcerative Colitis in Children", Postgrad. Med. *17*: 127 (Feb.) 1955.
3. MORRISON, L. M.: "Response of Ulcerative Colitis to Therapy with Salicylazosulfapyridine", J. A. M. A. *151*: 366 (Jan. 31) 1953.

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1. Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: *J.A.M.A.*, 158:625, June 25, 1955.
2. Schwab, R.S.: *Am. Jour. Med.*, 19:734, Nov., 1955.

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[1]Posner, A. C., *et al.*; Further Observations on the Use of Tetracycline Hydrochloride in Prophylaxis and Treatment of Obstetric Infections, *Antibiotics Annual* 1954-55, pp. 594-598.

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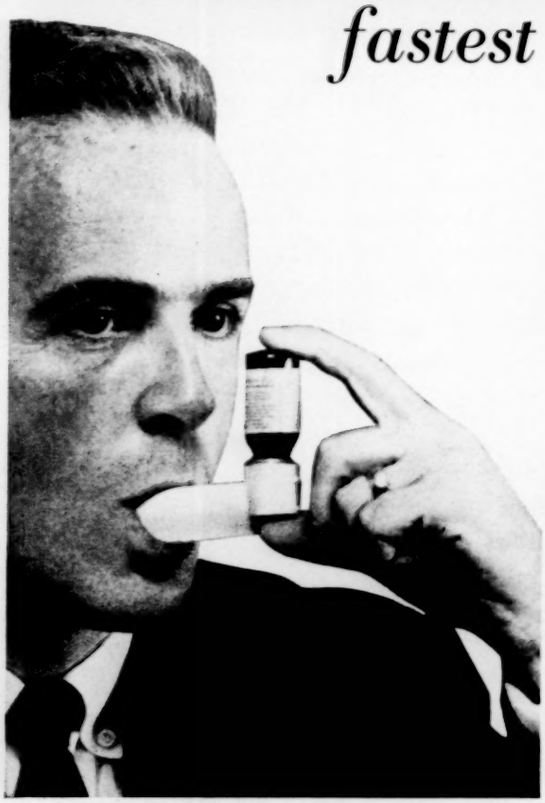
references: (1) Rottino, A.: Journal-Lancet *71*:237, 1951. (2) Susinno, A. M., and Verdon, R. E.: J.A.M.A. *154*:239 (Jan. 16), 1954.

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(1) Abrahamsen, E. H., and Baird, H. W., III: J.A.M.A. *160*:749 (Mar. 3) 1956.
(2) Amols, W.: J.A.M.A. *160*:742 (Mar. 3) 1956.
(3) Rodriguez-Gomez, M.; Valdes-Rodriguez, A., and Drew, A. L.: J.A.M.A. *160*:752 (Mar. 3) 1956.
(4) Smith, R. T.; Kron, K. M.; Peak, W. P., and Hermann, I. F.: J.A.M.A. *160*:745 (Mar. 3) 1956.

*T.M. †U. S. Patent Pending

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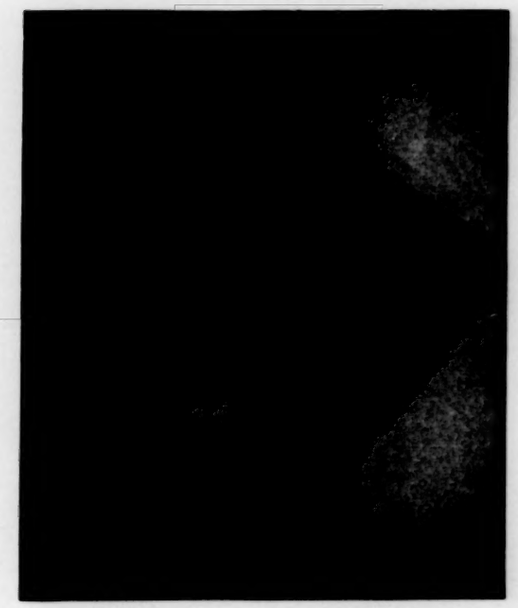
Contraindications: To be used with caution in patients with peptic ulcer, mental depression, cardiac conditions and related disorders.

Literature and Samples on Request

[1]Feinblatt, T.M., Feinblatt, H.M., and Ferguson, E.A.: Rauwolfia-Ephedrine, As a Hypotensive-Tranquilizer. J.A.M.A. *161*:424 (June 2, 1956).

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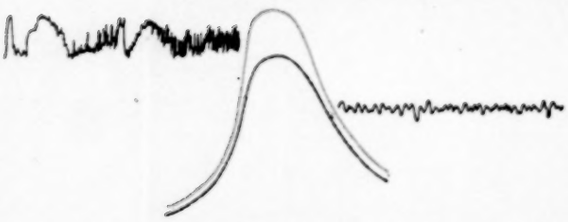
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1. Doyle, P. J., and Livingston, S.: J. Pediat. *43*:413 (Oct.) 1953.
2. Livingston, S., and Petersen, D.: To be published.
3. Pence, L. M.: Texas State J. Med. *50*:290 (May) 1954.

LITERATURE ON REQUEST

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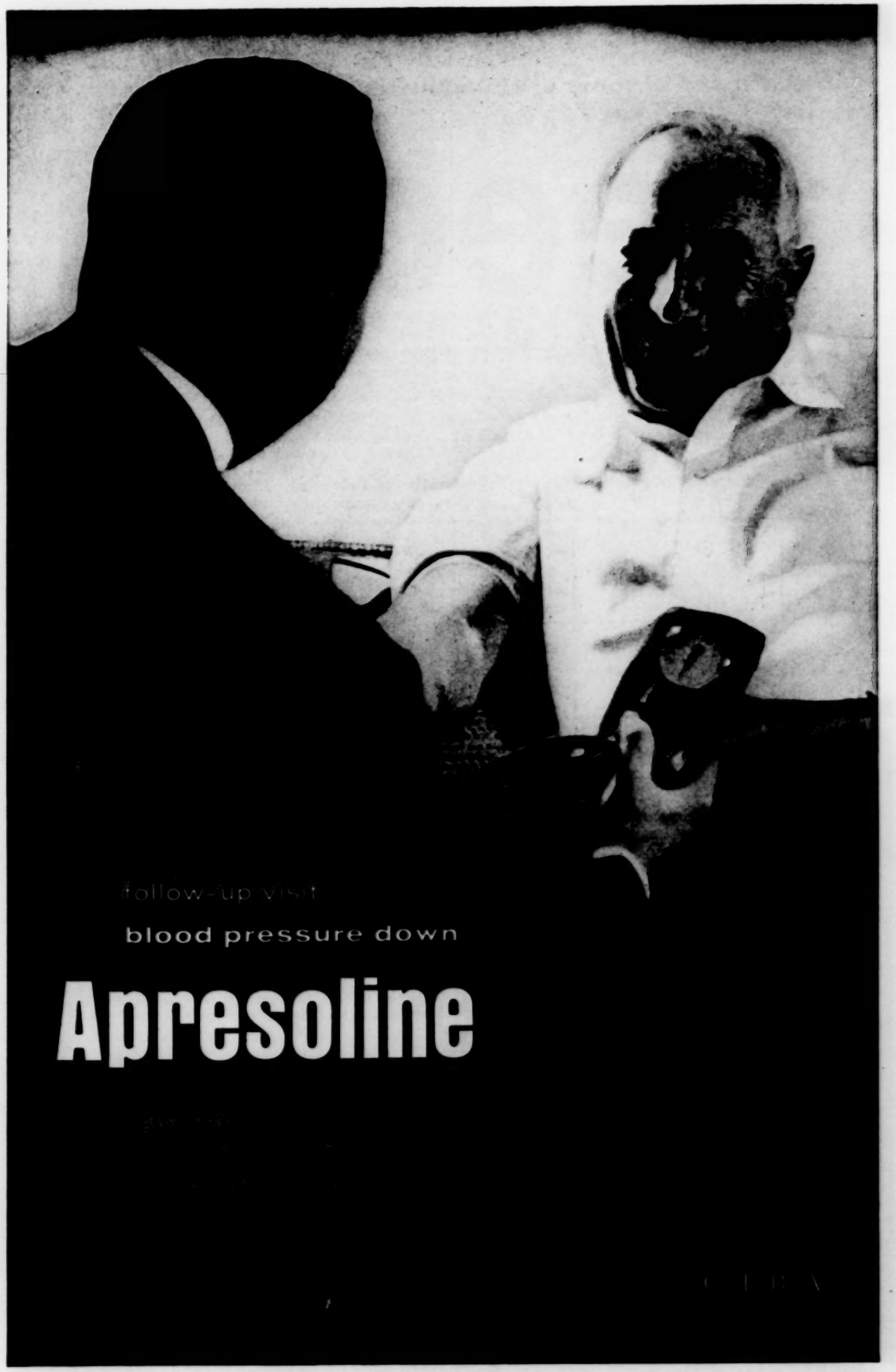
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Microorganism	Total no. strains	Sensitive*		Moderately sensitive*		Resistant*	
		No.	Per cent of total	No.	Per cent of total	No.	Per cent of total
Proteus vulgaris	237	209	88.2	28	11.8	0	0
Escherichia coli (including paracolon bacillus)	281	255	92.7	23	8.2	3	1.1
Aerobacter aerogenes	223	183	82.1	40	17.9	0	0
Streptococcus faecalis	160	155	96.7	5	3.1	0	0
Pseudomonas aeruginosa	101	5	5.0	40	39.9	56	55.4
Micrococcus pyogenes var. aureus	6	6	100	0	0	0	0
Klebsiella pneumoniae	3	3	100	0	0	0	0
Alcaligenes faecalis	2	2	100	0	0	0	0

*Organisms inhibited by 100 μg./ml. or less are classified as sensitive, by 200 to 400 μg./ml. as moderately sensitive, and those not inhibited by 400 μg./ml. as resistant.

"The status of P. vulgaris and of M. pyogenes var. aureus is especially noteworthy in the light of the high degree of resistance exhibited by those organisms to antibiotics currently employed."[3]

REFERENCES: 1. Trafton, H. M., et al.: N. England J. M. **252**:383, 1955. 2. Waisbren, B. A., and Crowley, W.: A. M. A. Arch. Int. M. **95**:653, 1955. 3. Schneierson, S. S.: Antibiotics **3**:212, 1956.

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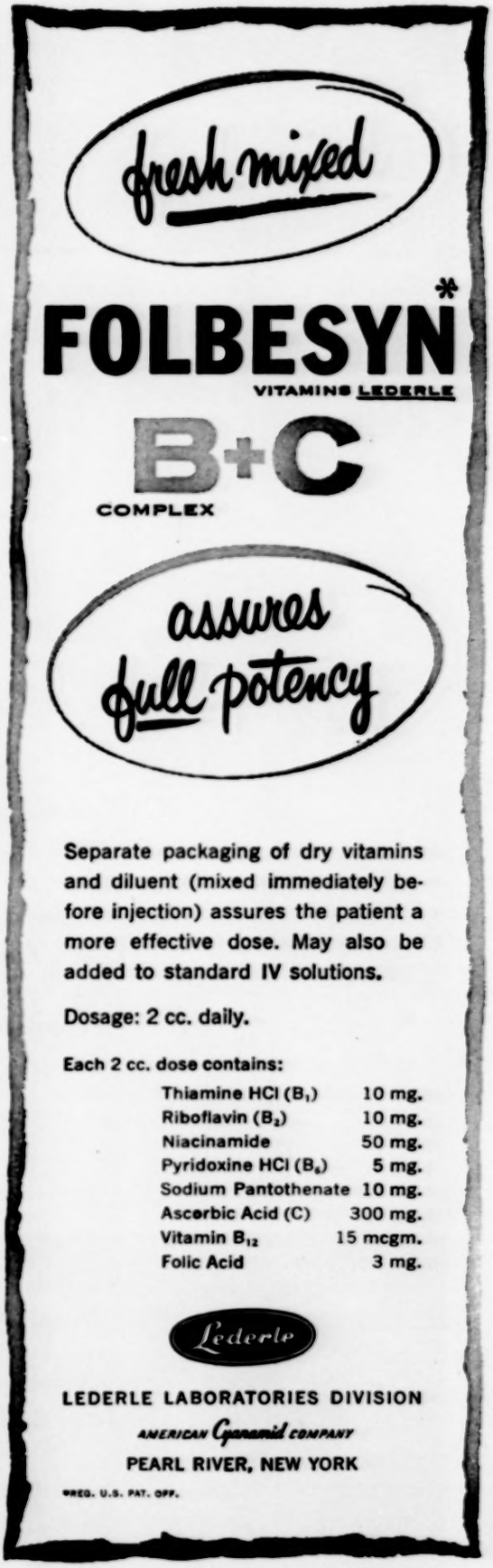
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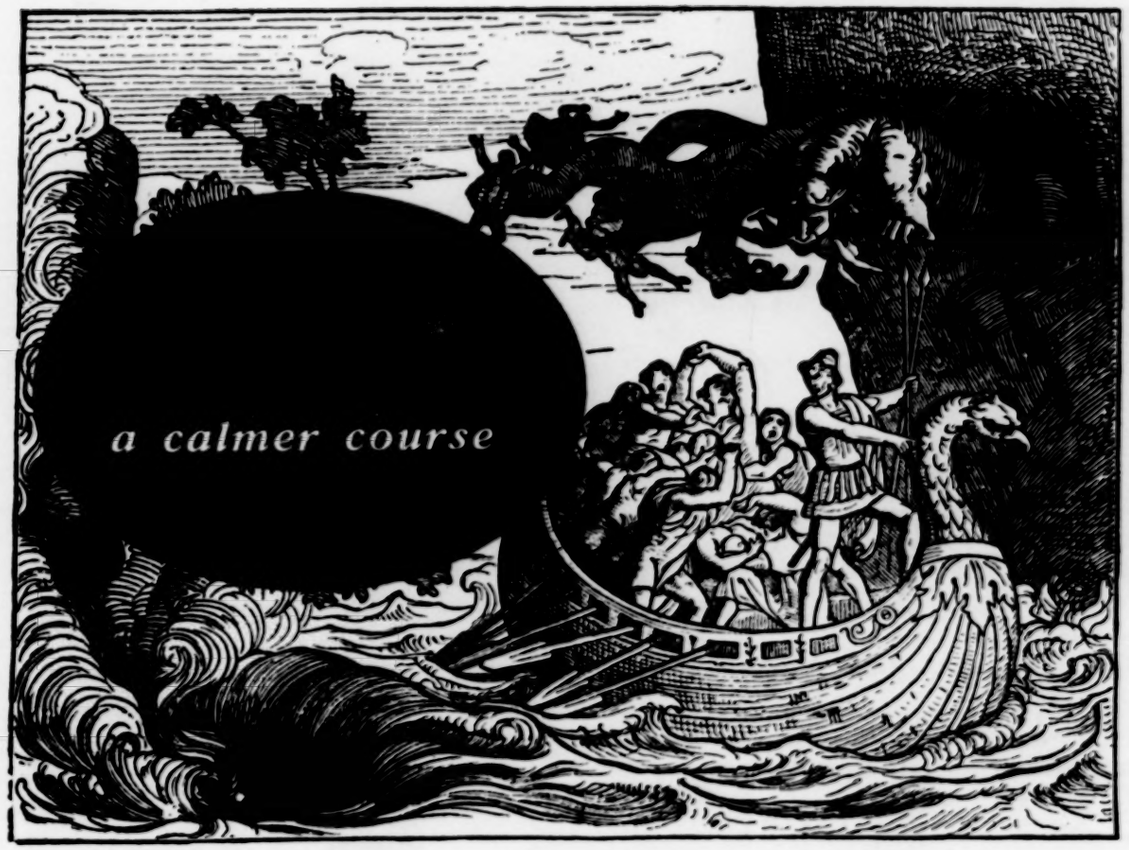
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[1] *Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med.* 11:*1105*

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Ritalin is a mild, safer central-nervous-system stimulant which gently improves mood, relieves psychogenic fatigue "without let-down or jitters . . ."[1] and counteracts oversedation caused by barbiturates, tranquilizing agents and antihistamines.

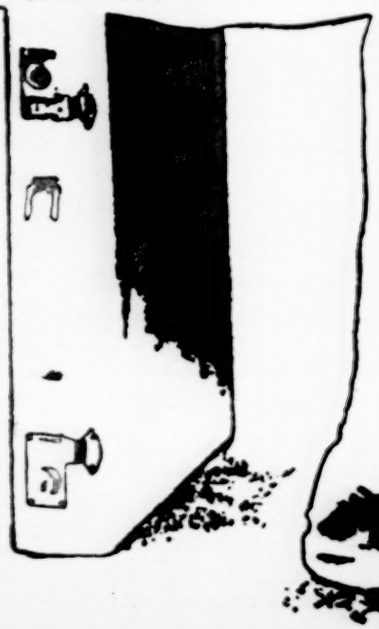
Ritalin is not an amphetamine. Except in rare instances it does not produce jitteriness or depressive rebound, and has little or no effect on blood pressure, pulse rate or appetite.

Reference: 1. Pocock, D. G.: Personal communication.

RITALIN® hydrochloride (methyl-phenidylacetate hydrochloride CIBA)

Average dosage: 10 mg. b.i.d. or t.i.d. Although individualization of dosage is always of paramount importance, the high relative safety of Ritalin permits larger doses for greater effect if necessary.

Supplied: Tablets, 5 mg. (yellow) and 10 mg. (blue); bottles of 100, 500 and 1000. Tablets, 20 mg. (peach-colored); bottles of 100 and 1000.



CIBA
SUMMIT, N.J.